

HARPER'S ILLUSTRATED BIOCHEMISTRY

INTERNATIONAL EDITION

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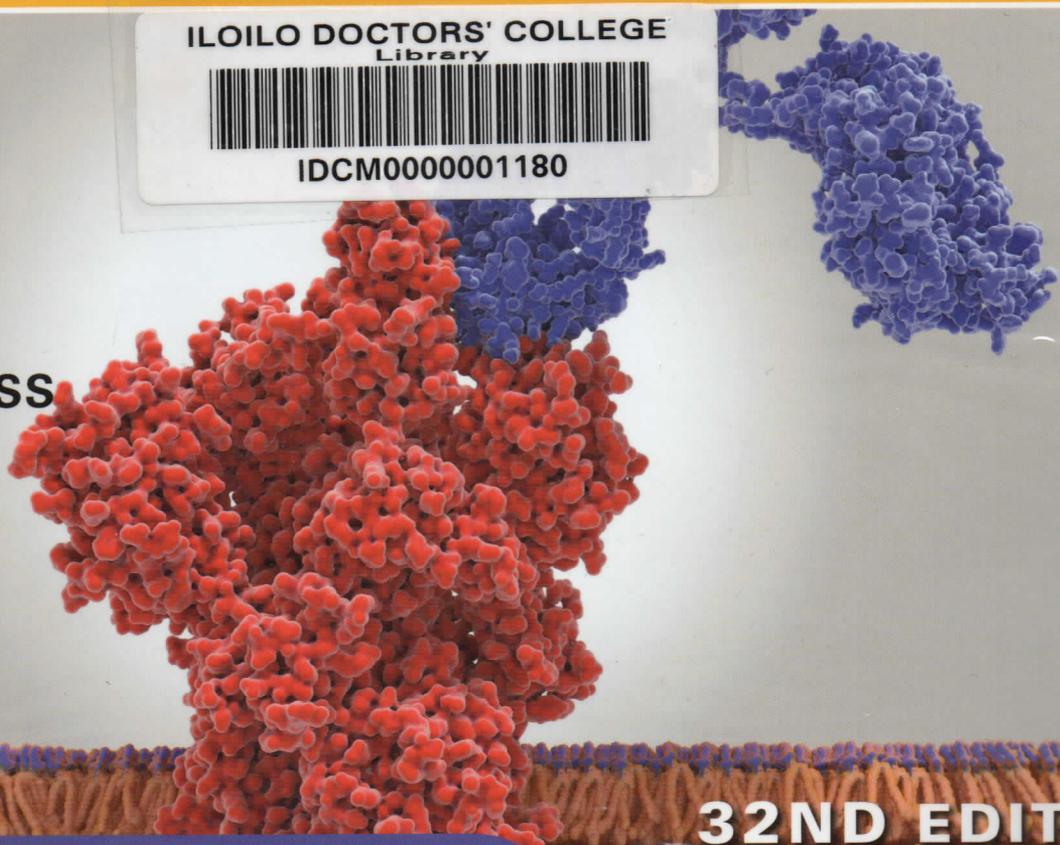
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Harper's

Illustrated Biochemistry

THIRTY-SECOND EDITION

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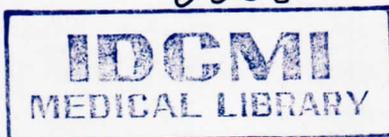
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Harper's Illustrated Biochemistry, Thirty-second Edition

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Contents

Preface ix

SECTION I

Structures & Functions of Proteins & Enzymes 1

- 1 Biochemistry & Medicine 1**
Victor W. Rodwell, PhD
- 2 Water & pH 6**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD
- 3 Amino Acids & Peptides 15**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD
- 4 Proteins: Determination of Primary Structure 24**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD
- 5 Proteins: Higher Orders of Structure 34**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD

SECTION II

Enzymes: Kinetics, Mechanism, Regulation, & Role of Transition Metals 49

- 6 Proteins: Myoglobin & Hemoglobin 49**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD
- 7 Enzymes: Mechanism of Action 59**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD
- 8 Enzymes: Kinetics 71**
Victor W. Rodwell, PhD
- 9 Enzymes: Regulation of Activities 85**
Peter J. Kennelly, PhD, & Victor W. Rodwell, PhD

10 The Biochemical Roles of Transition Metals 96

Peter J. Kennelly, PhD

SECTION III

Bioenergetics 109

- 11 Bioenergetics: The Role of ATP 109**
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 12 Biologic Oxidation 115**
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 13 The Respiratory Chain & Oxidative Phosphorylation 121**
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc

SECTION IV

Metabolism of Carbohydrates 133

- 14 Overview of Metabolism & the Provision of Metabolic Fuels 133**
Owen P. McGuinness, PhD
- 15 Saccharides (ie, Carbohydrates) of Physiological Significance 147**
Owen P. McGuinness, PhD
- 16 The Citric Acid Cycle: A Pathway Central to Carbohydrate, Lipid, & Amino Acid Metabolism 156**
Owen P. McGuinness, PhD

- 17** Glycolysis & the Oxidation of Pyruvate 163
Owen P. McGuinness, PhD
- 18** Metabolism of Glycogen 171
Owen P. McGuinness, PhD
- 19** Gluconeogenesis & the Control of Blood Glucose 180
Owen P. McGuinness, PhD
- 20** The Pentose Phosphate Pathway & Other Pathways of Hexose Metabolism 191
Owen P. McGuinness, PhD

SECTION

V

Metabolism of Lipids 205

- 21** Lipids of Physiologic Significance 205
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 22** Oxidation of Fatty Acids: Ketogenesis 217
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 23** Biosynthesis of Fatty Acids & Eicosanoids 226
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 24** Metabolism of Acylglycerols & Sphingolipids 239
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 25** Lipid Transport & Storage 247
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc
- 26** Cholesterol Synthesis, Transport, & Excretion 259
Kathleen M. Botham, PhD, DSc, & Peter A. Mayes, PhD, DSc

SECTION

VI

Metabolism of Proteins & Amino Acids 273

- 27** Biosynthesis of the Nutritionally Nonessential Amino Acids 273
Victor W. Rodwell, PhD

- 28** Catabolism of Proteins & of Amino Acid Nitrogen 279
Victor W. Rodwell, PhD

- 29** Catabolism of the Carbon Skeletons of Amino Acids 290
Victor W. Rodwell, PhD

- 30** Conversion of Amino Acids to Specialized Products 306
Victor W. Rodwell, PhD

- 31** Porphyrins & Bile Pigments 315
Victor W. Rodwell, PhD

SECTION

VII

Structure, Function, & Replication of Informational Macromolecules 329

- 32** Nucleotides 329
Victor W. Rodwell, PhD
- 33** Metabolism of Purine & Pyrimidine Nucleotides 337
Victor W. Rodwell, PhD
- 34** Nucleic Acid Structure & Function 348
P. Anthony Weil, PhD
- 35** DNA Organization, Replication, & Repair 360
P. Anthony Weil, PhD
- 36** RNA Synthesis, Processing, & Modification 384
P. Anthony Weil, PhD
- 37** Protein Synthesis & the Genetic Code 404
P. Anthony Weil, PhD
- 38** Regulation of Gene Expression 420
P. Anthony Weil, PhD
- 39** Molecular Genetics, Recombinant DNA, & Genomic Technology 444
P. Anthony Weil, PhD

SECTION

VIII

**Biochemistry of
Extracellular & Intracellular
Communication 467**

- 40** Membranes: Structure & Function 467
P. Anthony Weil, PhD
- 41** The Diversity of the Endocrine System 488
P. Anthony Weil, PhD
- 42** Hormone Action & Signal Transduction 508
P. Anthony Weil, PhD

SECTION

IX

Special Topics (A) 527

- 43** Nutrition, Digestion, & Absorption 527
David A. Bender, PhD
- 44** Micronutrients: Vitamins & Minerals 535
David A. Bender, PhD
- 45** Free Radicals & Antioxidant Nutrients 549
David A. Bender, PhD
- 46** Glycoproteins 554
David A. Bender, PhD
- 47** Metabolism of Xenobiotics 564
David A. Bender, PhD & Robert K. Murray, MD, PhD
- 48** Clinical Biochemistry 568
David A. Bender, PhD

SECTION

X

Special Topics (B) 581

- 49** Intracellular Traffic & Sorting of Proteins 581
Kathleen M. Botham, PhD, DSc, & Robert K. Murray, MD, PhD
- 50** The Extracellular Matrix 599
Kathleen M. Botham, PhD, DSc, & Robert K. Murray, MD, PhD
- 51** Muscle & the Cytoskeleton 618
January D. Haile, PhD, & Peter J. Kennelly, PhD
- 52** Plasma Proteins & Immunoglobulins 634
Peter J. Kennelly, PhD
- 53** Red Blood Cells 653
Peter J. Kennelly, PhD
- 54** White Blood Cells 664
Peter J. Kennelly, PhD

SECTION

XI

Special Topics (C) 677

- 55** Hemostasis & Thrombosis 677
*Peter L. Gross, MD, MSc, FRCP(C),
P. Anthony Weil, PhD, & Margaret L. Rand, PhD*
- 56** Cancer: An Overview 689
*Molly Jacob, MD, PhD, MNASC, FRCPATH,
Joe Varghese, MD, PhD, & P. Anthony Weil, PhD*
- 57** The Biochemistry of Aging 717
Peter J. Kennelly, PhD
- 58** Biochemical Case Histories 729
David A. Bender, PhD
- The Answer Bank 741
- Index 745

Preface

The authors and publishers are pleased to present the thirty-second edition of *Harper's Illustrated Biochemistry*. The first edition, entitled *Harper's Biochemistry*, was published in 1939 under the sole authorship of Dr Harold Harper at the University of California School of Medicine, San Francisco, California. Presently entitled *Harper's Illustrated Biochemistry*, the book continues, as originally intended, to provide a concise survey of aspects of biochemistry most relevant to the study of medicine. Various authors have contributed to subsequent editions of this medically oriented biochemistry text, which is now observing its 83rd year.

Cover Illustration for the Thirty-Second Edition

The global COVID-19 pandemic has provided a dramatic, face-to-face demonstration of both the power and limitations of molecular medicine and epidemiology. The rapid development of highly effective vaccines was made possible by the adaptation of novel RNA-based approaches in which the patient's immune response is activated via the endogenous expression of genetically-encoded antigens, rather than the physical injection of a non-infectious antigen. Utilizing the patient's own cells as the bioreactor for generating antigens, rather than some animal or culture, enabled scientists to use the self-amplifying capacity of polynucleotides to accelerate both the speed of vaccine development and subsequent large-scale manufacture. The illustration on the cover of the thirty-second edition depicts a neutralizing antibody, in blue, bound to the spike protein on the surface of the SARS-CoV-2 coronavirus, better known as COVID-19, which is shown in red. The epitope to which the antibody binds overlaps that at which the virus binds to the ACE-2 receptor, the membrane protein by which the pathogen recognizes, binds to, and subsequently invades human cells. Therapeutic antibodies thus protect by physically blocking association of the Spike protein with the ACE-2 receptor.

Changes in the Thirty-Second Edition

As always, *Harper's Illustrated Biochemistry* continues to emphasize the close relationship of biochemistry to the understanding of diseases, their pathology, and the practice of medicine. With the retirement of long-time contributor David A. Bender, Prof. Owen P. McGuinness of Vanderbilt University has joined as a new coauthor. In addition to the fresh perspectives and novel insights provided by Prof. McGuinness, the contents of most chapters have been updated and provide the reader with the most current and pertinent information.

For example, in Chapter 6 the description of the Bohr effect's contributions to CO₂ transport and release from the lungs has been reorganized and expanded, while Chapter 9 has been updated and reorganized to include expanded coverage of zymogen activation in enzyme regulation.

Organization of the Book

All 58 chapters of the thirty-second edition place major emphasis on the medical relevance of biochemistry. Topics are organized under 11 major headings. In order to assist study and to facilitate retention of the contained information, Questions follow each Section. An Answer Bank follows Chapter 58.

Section I includes a brief history of biochemistry and emphasizes the interrelationships between biochemistry and medicine. Water and the importance of homeostasis of intracellular pH are reviewed, and the various orders of proteins structure are addressed.

Section II begins with a chapter on hemoglobin. The next four chapters address the mechanism of action, kinetics, metabolic regulation of enzymes, and the role of metal ions in multiple aspects of intermediary metabolism.

Section III addresses bioenergetics and the role of high-energy phosphates in energy capture and transfer, the oxidation–reduction reactions involved in biologic oxidation, and metabolic details of energy capture via the respiratory chain and oxidative phosphorylation.

Section IV considers the metabolism of carbohydrates via glycolysis, the citric acid cycle, the pentose phosphate pathway, glycogen metabolism, gluconeogenesis, and the control of blood glucose.

Section V outlines the nature of simple and complex lipids, lipid transport and storage, the biosynthesis and degradation of fatty acids and more complex lipids, and the reactions and metabolic regulation of cholesterol biosynthesis and transport in human subjects.

Section VI discusses protein catabolism, urea biosynthesis, and the catabolism of amino acids, and stresses the medically significant metabolic disorders associated with their incomplete catabolism. The final chapter in this section considers the biochemistry of the porphyrins and bile pigments.

Section VII first outlines the structure and function of nucleotides and nucleic acids, and then details DNA replication and repair, RNA synthesis and modification, protein synthesis, the principles of recombinant DNA technology, and the regulation of gene expression.

Section VIII considers aspects of extracellular and intracellular communication. Specific topics include membrane structure and function, the molecular bases of the actions of hormones, and signal transduction.

Sections IX, X, and XI address many topics of significant medical importance.

Section IX discusses nutrition, digestion, and absorption, micronutrients including, vitamins, free radicals and antioxidants, glycoproteins, the metabolism of xenobiotics, and clinical biochemistry.

Section X addresses intracellular traffic and the sorting of proteins, the extracellular matrix, muscle and the cytoskeleton, plasma proteins and immunoglobulins, and the biochemistry of red cells and of white cells.

Section XI includes hemostasis and thrombosis, an overview of cancer, the biochemistry of aging, and a selection of case histories.

Acknowledgments

The authors thank Michael Weitz for his role in the planning of this edition and Peter Boyle for overseeing its preparation for publication. We also thank Tasneem Kauser and her colleagues at KnowledgeWorks Global Ltd. for their efforts in managing editing, typesetting, and artwork. We gratefully acknowledge numerous suggestions and corrections received from students and colleagues from around the world.

Peter J. Kennelly
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Changes in the Thirty-Second Edition

As always, further research continuously continues to emphasize the close relationship of biochemistry to the understanding of disease, the pathophysiology, and the practice of medicine. With the retirement of long-time coauthor David A. Bender, Fred Ojeda, R. McQuinn, and Jennifer L. University has joined as a new coauthor. In addition to the book's previous and newly included insights provided by Fred McQuinn, the contents of most chapters have been updated and provide the reader with the most current and pertinent information.

Structures & Functions of Proteins & Enzymes

1

Biochemistry & Medicine

Victor W. Rodwell, PhD

OBJECTIVES

After studying this chapter,
you should be able to:

- Understand the importance of the ability of cell-free extracts of yeast to ferment sugars, an observation that enabled discovery of the intermediates of fermentation, glycolysis, and other metabolic pathways.
- Appreciate the scope of biochemistry and its central role in the life sciences, and that biochemistry and medicine are intimately related disciplines.
- Appreciate that biochemistry integrates knowledge of the chemical processes in living cells with strategies to maintain health, understand disease, identify potential therapies, and enhance our understanding of the origins of life on earth.
- Describe how genetic approaches have been critical for elucidating many areas of biochemistry, and how the Human Genome Project has furthered advances in numerous aspects of biology and medicine.

BIOMEDICAL IMPORTANCE

Biochemistry and medicine enjoy a mutually cooperative relationship. Biochemical studies have illuminated many aspects of health and disease, and the study of various aspects of health and disease has opened up new areas of biochemistry. The medical relevance of biochemistry both in normal and abnormal situations is emphasized throughout this book. Biochemistry makes significant contributions to the fields of cell biology, physiology, immunology, microbiology, pharmacology, toxicology, and epidemiology, as well as the fields of inflammation, cell injury, and cancer. These close relationships emphasize that life, as we know it, depends on biochemical reactions and processes.

DISCOVERY THAT A CELL-FREE EXTRACT OF YEAST CAN FERMENT SUGAR

Although the ability of yeast to “ferment” various sugars to ethyl alcohol has been known for millennia, only comparatively recently did this process initiate the science of biochemistry. The great French microbiologist Louis Pasteur maintained that fermentation could only occur in intact cells. However, in 1899, the brothers Büchner discovered that fermentation could occur in the *absence* of intact cells when they stored a yeast extract in a crock of concentrated sugar solution, added as a preservative. Overnight, the contents of the crock fermented, spilled over the laboratory bench and floor,

and dramatically demonstrated that fermentation can proceed in the absence of an intact cell. This discovery unleashed an avalanche of research that initiated the science of biochemistry. Investigations revealed the vital roles of inorganic phosphate, ADP, ATP, and NAD(H), and ultimately identified the phosphorylated sugars and the chemical reactions and enzymes that convert glucose to pyruvate (glycolysis) or to ethanol and CO₂ (fermentation). Research beginning in the 1930s identified the intermediates of the citric acid cycle and of urea biosynthesis, and revealed the essential roles of certain vitamin-derived cofactors or “coenzymes” such as thiamin pyrophosphate, riboflavin, and ultimately coenzyme A, coenzyme Q, and cobamide coenzyme. The 1950s revealed how complex carbohydrates are synthesized from, and broken down into simple sugars, and the pathways for biosynthesis of pentoses, and the catabolism of amino acids and fatty acids.

Investigators employed animal models, perfused intact organs, tissue slices, cell homogenates and their subfractions, and subsequently purified enzymes. Advances were enhanced by the development of analytical ultracentrifugation, paper and other forms of chromatography, and the post-World War II availability of radioisotopes, principally ¹⁴C, ³H, and ³²P, as “tracers” to identify the intermediates in complex pathways such as that of cholesterol biosynthesis. X-ray crystallography was then used to solve the three-dimensional structures of numerous proteins, polynucleotides, enzymes, and viruses. Genetic advances that followed the realization that DNA was a double helix include the polymerase chain reaction, and transgenic animals or those with gene knockouts. The methods used to prepare, analyze, purify, and identify metabolites and the activities of natural and recombinant enzymes and their three-dimensional structures are discussed in the following chapters.

BIOCHEMISTRY & MEDICINE HAVE PROVIDED MUTUAL ADVANCES

The two major concerns for workers in the health sciences—and particularly physicians—are the understanding and maintenance of health and effective treatment of disease. Biochemistry impacts both of these fundamental concerns, and

the interrelationship of biochemistry and medicine is a wide, two-way street. Biochemical studies have illuminated many aspects of health and disease, and conversely, the study of various aspects of health and disease has opened up new areas of biochemistry (**Figure 1–1**). An early example of how investigation of protein structure and function revealed the single difference in amino acid sequence between normal hemoglobin and sickle cell hemoglobin. Subsequent analysis of numerous variant sickle cell and other hemoglobins has contributed significantly to our understanding of the structure and function both of hemoglobin and of other proteins. During the early 1900s, the English physician Archibald Garrod studied patients with the relatively rare disorders of alkaptonuria, albinism, cystinuria, and pentosuria, and established that these conditions were genetically determined. Garrod designated these conditions as **inborn errors of metabolism**. His insights provided a foundation for the development of the field of human biochemical genetics. A more recent example was investigation of the genetic and molecular basis of familial hypercholesterolemia, a disease that results in early-onset atherosclerosis. In addition to clarifying different genetic mutations responsible for this disease, this provided a deeper understanding of cell receptors and mechanisms of uptake, not only of cholesterol but also of how other molecules cross cell membranes. Studies of **oncogenes** and **tumor suppressor genes** in cancer cells have directed attention to the molecular mechanisms involved in the control of normal cell growth. These examples illustrate how the study of disease can open up areas of basic biochemical research. Science provides physicians and other workers in health care and biology with a foundation that impacts practice, stimulates curiosity, and promotes the adoption of scientific approaches for continued learning.

BIOCHEMICAL PROCESSES UNDERLIE HUMAN HEALTH

Biochemical Research Impacts Nutrition & Preventive Medicine

The World Health Organization (WHO) defines health as a state of “complete physical, mental, and social well-being and not merely the absence of disease and infirmity.” From a biochemical

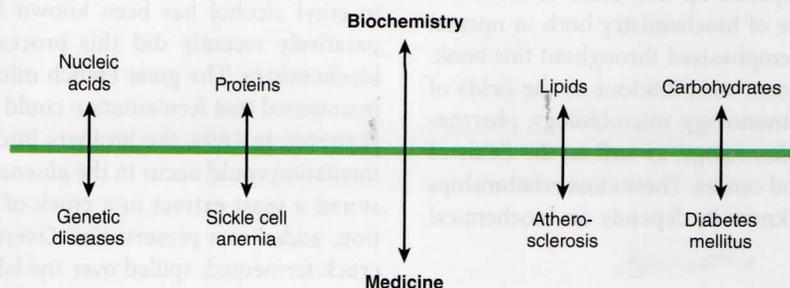


FIGURE 1–1 A two-way street connects biochemistry and medicine. Knowledge of the biochemical topics listed above the green line of the diagram has clarified our understanding of the diseases shown below the green line. Conversely, analyses of the diseases have cast light on many areas of biochemistry. Note that sickle cell anemia is a genetic disease, and that both atherosclerosis and diabetes mellitus have genetic components.

viewpoint, health may be considered that situation in which all of the many thousands of intra- and extracellular reactions that occur in the body are proceeding at rates commensurate with the organism's survival under pressure from both internal and external challenges. The maintenance of health requires optimal dietary intake of **vitamins**, certain **amino acids** and **fatty acids**, various **minerals**, and **water**. Understanding nutrition depends to a great extent on knowledge of biochemistry, and the sciences of biochemistry and nutrition share a focus on these chemicals. Recent increasing emphasis on systematic attempts to maintain health and forestall disease, or **preventive medicine**, includes nutritional approaches to the prevention of diseases such as atherosclerosis and cancer.

Most Diseases Have a Biochemical Basis

Apart from infectious organisms and environmental pollutants, many diseases are manifestations of abnormalities in genes, proteins, chemical reactions, or biochemical processes, each of which can adversely affect one or more critical biochemical functions. Examples of disturbances in human biochemistry responsible for diseases or other debilitating conditions include electrolyte imbalance, defective nutrient ingestion or absorption, hormonal imbalances, toxic chemicals or biologic agents, and DNA-based genetic disorders. To address these challenges, biochemical research continues to be interwoven with studies in disciplines such as genetics, cell biology, immunology, nutrition, pathology, and pharmacology. In addition, many biochemists are vitally interested in contributing to solutions to key issues such as the ultimate survival of mankind, and educating the public to support use of the scientific method in solving environmental and other major problems that confront our civilization.

Impact of the Human Genome Project on Biochemistry, Biology, & Medicine

Initially unanticipated rapid progress in the late 1990s in sequencing the human genome led in the mid-2000s to the

announcement that over 90% of the genome had been sequenced. This effort was headed by the International Human Genome Sequencing Consortium and by Celera Genomics. Except for a few gaps, the sequence of the entire human genome was completed in 2003, just 50 years after the description of the double-helical nature of DNA by Watson and Crick. The implications for biochemistry, medicine, and indeed for all of biology, are virtually unlimited. For example, the ability to isolate and sequence a gene and to investigate its structure and function by sequencing and “gene knockout” experiments have revealed previously unknown genes and their products, and new insights have been gained concerning human evolution and procedures for identifying disease-related genes.

Major advances in biochemistry and understanding human health and disease continue to be made by mutation of the genomes of model organisms such as yeast, the fruit fly *Drosophila melanogaster*, the roundworm *Caenorhabditis elegans*, and the zebra fish; all organisms that can be genetically manipulated to provide insight into the functions of individual genes. These advances can potentially provide clues to curing human diseases such as cancer and Alzheimer disease. **Figure 1–2** highlights areas that have developed or accelerated as a direct result of progress made in the Human Genome Project (HGP). New “-omics” fields focus on comprehensive study of the structures and functions of the molecules with which each is concerned. The products of genes (RNA molecules and proteins) are being studied using the techniques of **transcriptomics** and **proteomics**. A spectacular example of the speed of progress in transcriptomics is the explosion of knowledge about small RNA molecules as regulators of gene activity. Other -omics fields include **glycomics**, **lipidomics**, **metabolomics**, **nutrigenomics**, and **pharmacogenomics**. To keep pace with the information generated, **bioinformatics** has received much attention. Other related fields to which the impetus from the HGP has carried over are **biotechnology**, **bioengineering**, **biophysics**, and **bioethics**.

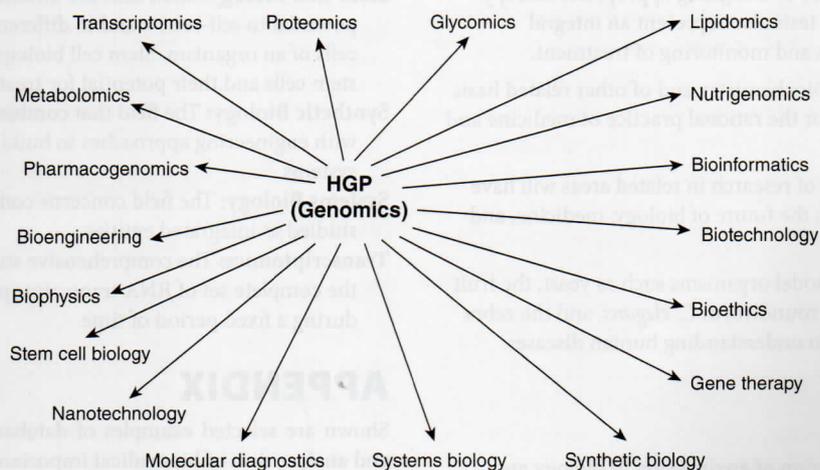


FIGURE 1–2 The Human Genome Project (HGP) has influenced many disciplines and areas of research. Biochemistry is not listed since it predates commencement of the HGP, but disciplines such as bioinformatics, genomics, glycomics, lipidomics, metabolomics, molecular diagnostics, proteomics, and transcriptomics are nevertheless active areas of biochemical research.

Definitions of these -omics fields and other terms appear in the Glossary of this chapter. **Nanotechnology** is an active area, which, for example, may provide novel methods of diagnosis and treatment for cancer and other disorders. **Stem cell biology** is at the center of much current research. **Gene therapy** has yet to deliver the promise that it appears to offer, but it seems probable that ultimately will occur. Many new **molecular diagnostic tests** have developed in areas such as genetic, microbiologic, and immunologic testing and diagnosis. **Systems biology** is also burgeoning. The outcomes of research in the various areas mentioned above will impact tremendously the future of biology, medicine, and the health sciences. **Synthetic biology** offers the potential for creating living organisms, initially small bacteria, from genetic material in vitro that might carry out specific tasks such as cleansing petroleum spills. All of the above make the 21st century an exhilarating time to be directly involved in biology and medicine.

SUMMARY

- Biochemistry is the science concerned with the molecules present in living organisms, individual chemical reactions and their enzyme catalysts, and the expression and regulation of each metabolic process. Biochemistry has become the basic language of all biologic sciences.
- Despite the focus on human biochemistry in this text, biochemistry concerns the entire spectrum of life forms, from viruses, bacteria, and plants to complex eukaryotes such as human beings.
- Biochemistry, medicine, and other health care disciplines are intimately related. Health in all species depends on a harmonious balance of the biochemical reactions occurring in the body, while disease reflects abnormalities in biomolecules, biochemical reactions, or biochemical processes.
- Advances in biochemical knowledge have illuminated many areas of medicine, and the study of diseases has often revealed previously unsuspected aspects of biochemistry.
- Biochemical approaches are often fundamental in illuminating the causes of diseases and in designing appropriate therapy. Biochemical laboratory tests also represent an integral component of diagnosis and monitoring of treatment.
- A sound knowledge of biochemistry and of other related basic disciplines is essential for the rational practice of medicine and related health sciences.
- Results of the HGP and of research in related areas will have a profound influence on the future of biology, medicine, and other health sciences.
- Genomic research on model organisms such as yeast, the fruit fly *D. melanogaster*, the roundworm *C. elegans*, and the zebra fish provides insight into understanding human diseases.

GLOSSARY

- Bioengineering:** The application of engineering to biology and medicine.
- Bioethics:** The area of ethics that is concerned with the application of moral and ethical principles to biology and medicine.

Bioinformatics: The discipline concerned with the collection, storage, and analysis of biologic data, for example, DNA, RNA, and protein sequences.

Biophysics: The application of physics and its techniques to biology and medicine.

Biotechnology: The field in which biochemical, engineering, and other approaches are combined to develop biologic products of use in medicine and industry.

Gene Therapy: Applies to the use of genetically engineered genes to treat various diseases.

Genomics: The genome is the complete set of genes of an organism, and genomics is the in-depth study of the structures and functions of genomes.

Glycomics: The glycome is the total complement of simple and complex carbohydrates in an organism. Glycomics is the systematic study of the structures and functions of glycomes such as the human glycome.

Lipidomics: The lipidome is the complete complement of lipids found in an organism. Lipidomics is the in-depth study of the structures and functions of all members of the lipidome and their interactions, in both health and disease.

Metabolomics: The metabolome is the complete complement of metabolites (small molecules involved in metabolism) present in an organism. Metabolomics is the in-depth study of their structures, functions, and changes in various metabolic states.

Molecular Diagnostics: Refers to the use of molecular approaches such as DNA probes to assist in the diagnosis of various biochemical, genetic, immunologic, microbiologic, and other medical conditions.

Nanotechnology: The development and application to medicine and to other areas of devices such as nanoshells, which are only a few nanometers in size (10^{-9} m = 1 nm).

Nutrigenomics: The systematic study of the effects of nutrients on genetic expression and of the effects of genetic variations on the metabolism of nutrients.

Pharmacogenomics: The use of genomic information and technologies to optimize the discovery and development of new drugs and drug targets.

Proteomics: The proteome is the complete complement of proteins of an organism. Proteomics is the systematic study of the structures and functions of proteomes and their variations in health and disease.

Stem Cell Biology: Stem cells are undifferentiated cells that have the potential to self-renew and to differentiate into any of the adult cells of an organism. Stem cell biology concerns the biology of stem cells and their potential for treating various diseases.

Synthetic Biology: The field that combines biomolecular techniques with engineering approaches to build new biologic functions and systems.

Systems Biology: The field concerns complex biologic systems studied as integrated entities.

Transcriptomics: The comprehensive study of the transcriptome, the complete set of RNA transcripts produced by the genome during a fixed period of time.

APPENDIX

Shown are selected examples of databases that assemble, annotate, and analyze data of biomedical importance.

ENCODE: ENCyclopedia Of DNA Elements. A collaborative effort that combines laboratory and computational approaches to identify every functional element in the human genome.

GenBank: Protein sequence database of the National Institutes of Health (NIH) stores all known biologic nucleotide sequences and their translations in a searchable form.

HapMap: Haplotype Map, an international effort to identify single nucleotide polymorphisms (SNPs) associated with common human diseases and differential responses to pharmaceuticals.

ISDB: International Sequence DataBase that incorporates DNA databases of Japan and of the European Molecular Biology Laboratory (EMBL).

PDB: Protein DataBase. Three-dimensional structures of proteins, polynucleotides, and other macromolecules, including proteins bound to substrates, inhibitors, or other proteins.