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CHAPTER

1

Biochemistry & Medicine

Robert K. Murray, MD, PhD

INTRODUCTION

Biochemistry can be defined as *the science of the chemical basis of life* (Gk *bios* "life"). The **cell** is the structural unit of living systems. Thus, biochemistry can also be described as *the science of the chemical constituents of living cells and of the reactions and processes they undergo.* By this definition, biochemistry encompasses large areas of **cell biology, molecular biology,** and **molecular genetics.**

The Aim of Biochemistry Is to Describe & Explain, in Molecular Terms, All Chemical Processes of Living Cells

The major objective of biochemistry is the complete understanding, at the molecular level, of all of the chemical processes associated with living cells. To achieve this objective, biochemists have sought to isolate the numerous molecules found in cells, determine their structures, and analyze how they function. Many techniques have been used for these purposes; some of them are summarized in Table 1–1.

A Knowledge of Biochemistry Is Essential to All Life Sciences

The biochemistry of the nucleic acids lies at the heart of **genetics;** in turn, the use of genetic approaches has been critical for elucidating many areas of biochemistry. **Physiology,** the study of body function, overlaps with biochemistry almost completely. **Immunology** employs numerous biochemical techniques, and many immunologic approaches have found wide use by biochemists. **Pharmacology** and **pharmacy** rest on a sound knowledge of biochemistry and physiology; in particular, most drugs are metabolized by enzyme-catalyzed reactions. Poisons act on biochemical reactions or processes; this is the subject matter of **toxicology.** Biochemical approaches are being used increasingly to study basic aspects of **pathology** (the study of disease), such as inflammation, cell injury, and cancer. Many workers in **microbiology, zoology,** and **botany** employ biochemical approaches almost exclusively. These relationships are not surprising, because life as we know it depends on biochemical reactions and processes. In fact, the old barriers among the life sciences are breaking down, and biochemistry is increasingly becoming their common language.

A Reciprocal Relationship Between Biochemistry & Medicine Has Stimulated Mutual Advances

The two major concerns for workers in the health sciences—and particularly physicians—are the understanding and maintenance of **health** and the understanding and effective treatment of **diseases.** Biochemistry impacts enormously on both of these fundamental concerns of medicine. In fact, 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. Some examples of this two-way street are shown in Figure 1–1. For instance, knowledge of protein structure and function was necessary to elucidate the single biochemical difference between normal hemoglobin and sickle cell hemoglobin. On the other hand, analysis of sickle cell hemoglobin has contributed significantly to our understanding of the structure and function of both normal hemoglobin and other proteins. Analogous examples of reciprocal benefit between biochemistry and medicine could be cited for the other paired items shown in Figure 1–1. Another example is the pioneering work of Archibald Garrod, a physician in England during the early 1900s. He studied patients with a number of relatively rare disorders (alkaptonuria, albinism, cystinuria, and pentosuria; these are described in later chapters) and established that these conditions were genetically determined. Garrod designated these conditions as **inborn errors of metabolism.** His insights provided a major foundation for the development of the field of human biochemical genetics. More recent efforts to understand the basis of the genetic disease known as **familial hypercholesterolemia,** which results in severe atherosclerosis at an early age, have led to dramatic progress in understanding of cell receptors and of mechanisms of uptake of cholesterol into cells. Studies of **oncogenes** in cancer cells have directed attention to the molecular mechanisms involved in the control of normal

TABLE 1–1 The Principal Methods and Preparations Used in Biochemical Laboratories

Methods for Separating and Purifying Biomolecules[1]
Salt fractionation (eg, precipitation of proteins with ammonium sulfate)
Chromatography: Paper, ion exchange, affinity, thin-layer, gas–liquid, high-pressure liquid, gel filtration
Electrophoresis: Paper, high-voltage, agarose, cellulose acetate, starch gel, polyacrylamide gel, SDS-polyacrylamide gel
Ultracentrifugation
Methods for Determining Biomolecular Structures
Elemental analysis
UV, visible, infrared, and NMR spectroscopy
Use of acid or alkaline hydrolysis to degrade the biomolecule under study into its basic constituents
Use of a battery of enzymes of known specificity to degrade the biomolecule under study (eg, proteases, nucleases, glycosidases)
Mass spectrometry
Specific sequencing methods (eg, for proteins and nucleic acids)
X-ray crystallography
Preparations for Studying Biochemical Processes
Whole animal (includes transgenic animals and animals with gene knockouts)
Isolated perfused organ
Tissue slice
Whole cells
Homogenate
Isolated cell organelles
Subfractionation of organelles
Purified metabolites and enzymes
Isolated genes (including polymerase chain reaction and site-directed mutagenesis)

[1]Most of these methods are suitable for analyzing the components present in cell homogenates and other biochemical preparations. The sequential use of several techniques will generally permit purification of most biomolecules. The reader is referred to texts on methods of biochemical research for details.

cell growth. These and many other examples emphasize how the study of disease can open up areas of cell function for basic biochemical research.

The relationship between medicine and biochemistry has important implications for the former. As long as medical treatment is firmly grounded in the knowledge of biochemistry and other basic sciences, the practice of medicine will have a rational basis that can be adapted to accommodate new knowledge. This contrasts with unorthodox health cults and at least some "alternative medicine" practices that are often founded on little more than myth and wishful thinking and generally lack any intellectual basis.

NORMAL BIOCHEMICAL PROCESSES ARE THE BASIS OF HEALTH

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 strictly biochemical 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 maximal survival in the physiologic state. However, this is an extremely reductionist view, and it should be apparent that caring for the health of patients requires not only a wide knowledge of biologic principles but also of psychologic and social principles.

Biochemical Research Has Impact on Nutrition & Preventive Medicine

One major prerequisite for the maintenance of health is that there be optimal dietary intake of a number of chemicals; the chief of these are **vitamins,** certain **amino acids,** certain **fatty acids,** various **minerals,** and **water.** Because much of the subject matter of both biochemistry and nutrition is concerned with the study of various aspects of these chemicals, there is a close relationship between these two sciences. Moreover, more emphasis is being placed on systematic attempts to maintain health and forestall disease, that is, on **preventive medicine.** Thus, nutritional approaches to—for example—the prevention of atherosclerosis and cancer are receiving increased emphasis. Understanding nutrition depends to a great extent on knowledge of biochemistry.

Most & Perhaps All Diseases Have a Biochemical Basis

We believe that most if not all diseases are manifestations of abnormalities of molecules, chemical reactions, or biochemical processes. The **major factors responsible for causing diseases** in animals and humans are listed in Table 1–2. All of them affect one or more critical chemical reactions or molecules in the body. Numerous examples of the biochemical bases of diseases will be encountered in this text. In most of these conditions, biochemical studies contribute to both the diagnosis and treatment. Some **major uses of biochemical investigations and of laboratory tests in relation to diseases** are summarized in Table 1–3. Chapter 54 of this text further helps to illustrate the relationship of biochemistry to disease by discussing in some detail biochemical aspects of 16 different medical cases.

Some of the **major challenges that medicine and related health sciences** face are also outlined very briefly at the end of Chapter 54. In addressing these challenges, biochemical studies are already and will continue to be interwoven with studies in various other disciplines, such as genetics, immunology, nutrition, pathology and pharmacology.

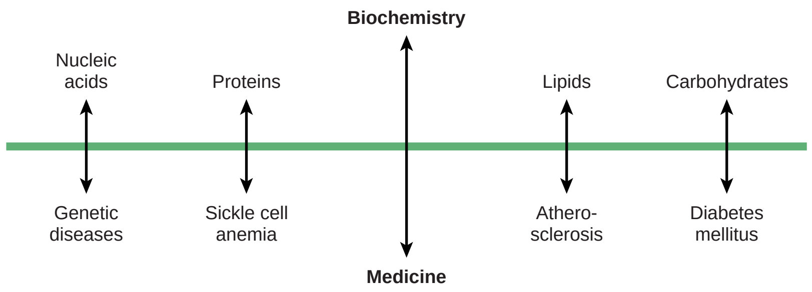

FIGURE 1–1 Examples of the two-way street connecting biochemistry and medicine. Knowledge of the biochemical molecules shown in the top part of the diagram has clarified our understanding of the diseases shown on the bottom half—and conversely, analyses of the diseases shown below have cast light on many areas of biochemistry. Note that sickle cell anemia is a genetic disease and that both atherosclerosis and diabetes mellitus have genetic components.

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

Remarkable progress was made in the late 1990s in sequencing the human genome by the HGP. This culminated in July 2000, when leaders of the two groups involved in this effort (the International Human Genome Sequencing Consortium and Celera Genomics, a private company) announced that over 90% of the genome had been sequenced. Draft versions of the sequence were published in early 2001. With the exception of a few gaps, the sequence of the entire human genome was completed in 2003, 50 years after the description of the double-helical nature of DNA by Watson and Crick.

The **implications** of the HGP for **biochemistry**, all of **biology**, and for **medicine** and **related health sciences** are tremendous, and only a few points are mentioned here. It is **now possible to isolate any gene and usually determine its structure and function** (eg, by sequencing and knockout experiments). Many **previously unknown genes** have been revealed; their products have already been established, or are under study. New light has been thrown on **human evolution**, and procedures for **tracking disease genes** have been greatly refined. Reference to the human genome will be made in various sections of this text.

Figure 1–2 shows **areas of great current interest** that have developed either directly as a result of the progress made in the HGP, or have been spurred on by it. As an outgrowth of the HGP, many so-called -**omics** fields have sprung up, involving comprehensive studies of the structures and functions of the molecules with which each is concerned. Definitions of the fields listed below are given in the Glossary of this

TABLE 1–2 The Major Causes of Diseases[1]

1. *Physical agents:* Mechanical trauma, extremes of temperature, sudden changes in atmospheric pressure, radiation, electric shock.
2. *Chemical agents, including drugs:* Certain toxic compounds, therapeutic drugs, etc.
3. *Biologic agents:* Viruses, bacteria, fungi, higher forms of parasites.
4. *Oxygen lack:* Loss of blood supply, depletion of the oxygen-carrying capacity of the blood, poisoning of the oxidative enzymes.
5. *Genetic disorders:* Congenital, molecular.
6. *Immunologic reactions:* Anaphylaxis, autoimmune disease.
7. *Nutritional imbalances:* Deficiencies, excesses.
8. *Endocrine imbalances:* Hormonal deficiencies, excesses.

[1]**Note:** All of the causes listed act by influencing the various biochemical mechanisms in the cell or in the body.

(Adapted, with permission, from Robbins SL, Cotram RS, Kumar V: *The Pathologic Basis of Disease,* 3rd ed. Saunders, 1984. Copyright © 1984 Elsevier Inc. with permission from Elsevier.)

TABLE 1–3 Some Uses of Biochemical Investigations and Laboratory Tests in Relation to Diseases

Use	Example
1. To reveal the fundamental causes and mechanisms of diseases	Demonstration of the nature of the genetic defects in cystic fibrosis.
2. To suggest rational treatments of diseases based on item 1 above	A diet low in phenylalanine for treatment of phenylketonuria.
3. To assist in the diagnosis of specific diseases	Use of the plasma levels of troponin I or T in the diagnosis of myocardial infarction.
4. To act as screening tests for the early diagnosis of certain diseases	Use of measurement of blood thyroxine or thyroid-stimulating hormone (TSH) in the neonatal diagnosis of congenital hypothyroidism.
5. To assist in monitoring the progress (ie, recovery, worsening, remission, or relapse) of certain diseases	Use of the plasma enzyme alanine aminotransferase (ALT) in monitoring the progress of infectious hepatitis.
6. To assist in assessing the response of diseases to therapy	Use of measurement of blood carcinoembryonic antigen (CEA) in certain patients who have been treated for cancer of the colon.

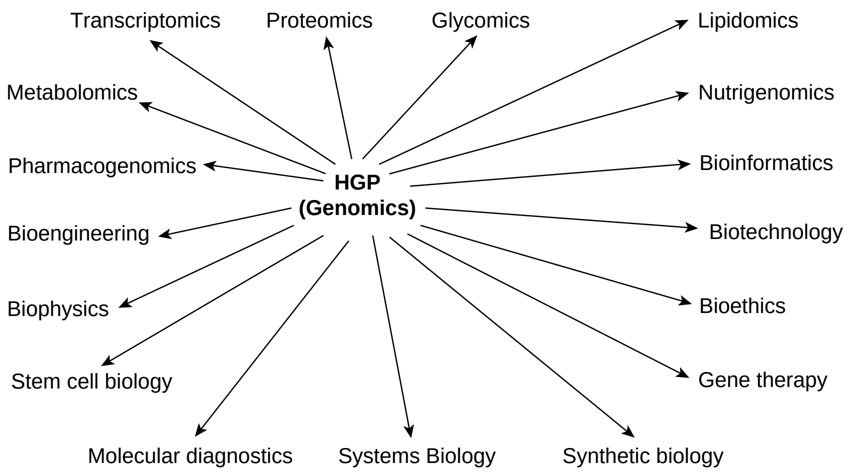

FIGURE 1–2 The Human Genome Project (HGP) has influenced many disciplines and areas of research.

chapter. The products of genes (RNA molecules and proteins) are being studied using the technics of **transcriptomics** and **proteomics**. One 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 amount of information being 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**. **Stem cell biology** is at the center of much current research. **Gene therapy** has yet to deliver the promise that it contains, but it seems probable that will occur sooner or later. Many new **molecular diagnostic tests** have developed in areas such as genetic, microbiologic, and immunologic testing and diagnosis. **Systems biology** is also burgeoning. **Synthetic biology** is perhaps the most intriguing of all. This has the potential for creating living organisms (eg, initially small bacteria) from genetic material in vitro. These could perhaps be designed to carry out specific tasks (eg, to mop up petroleum spills). As in the case of stem cells, this area will attract much attention from bioethicists and others. Many of the above topics are referred to later in this text.

All of the above have made the present time a very exciting one for studying or to be directly involved in biology and medicine. The outcomes of research in the various areas mentioned above will impact tremendously on the future of biology, medicine and the health sciences.

SUMMARY

- Biochemistry is the science concerned with studying the various molecules that occur in living cells and organisms and with their chemical reactions. Because life depends on biochemical reactions, biochemistry has become the basic language of all biologic sciences.
- Biochemistry is concerned with the entire spectrum of life forms, from relatively simple viruses and bacteria to complex human beings.
- Biochemistry and medicine are intimately related. Health depends on a harmonious balance of biochemical reactions occurring in the body, and disease reflects abnormalities in biomolecules, biochemical reactions, or biochemical processes.
- Advances in biochemical knowledge have illuminated many areas of medicine. Conversely, 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 therapies.
- The judicious use of various biochemical laboratory tests is 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.

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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, mainly DNA and protein sequences (see Chapter 10).

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

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

Gene Therapy: Applies to the use of genetically engineered genes to treat various diseases (see Chapter 39).

Genomics: The genome is the complete set of genes of an organism (eg, the human genome) and genomics is the in depth study of the structures and functions of genomes (see Chapter 10 and other chapters).

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 (eg, the human glycome; see Chapter 47).

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 of their interactions, in both health and disease.

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

Molecular Diagnostics: The use of molecular approaches (eg, DNA probes) to assist in the diagnosis of various biochemical, genetic, immunologic, microbiologic, and other medical conditions.

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

Pharmacogenomics: The use of genomic information and technologies to optimize the discovery and development of drug targets and drugs (see Chapter 54).

Proteomics: The proteome is the complete complement of proteins of an organism. Proteomics is the systematic study of the structures and functions of proteomes, including variations in health and disease (see Chapter 4).

Stem Cell Biology: A stem cell is an undifferentiated cell that has the potential to renew itself and to differentiate into any of the adult cells found in the organism. Stem cell biology is concerned with the biology of stem cells and their uses in various diseases.

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

Systems Biology: The field of science in which complex biologic systems are studied as integrated wholes (as opposed to the reductionist approach of, for example, classic biochemistry).

Transcriptomics: The transcriptome is the complete set of RNA transcripts produced by the genome at a fixed period in time. Transcriptomics is the comprehensive study of gene expression at the RNA level (see Chapter 36 and other chapters).