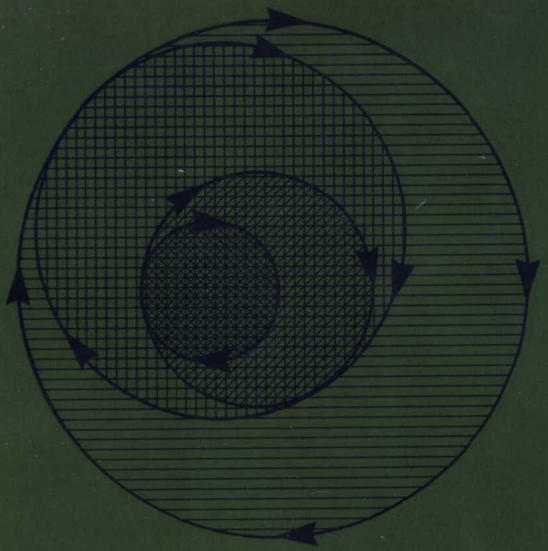

HUMAN BIOCHEMISTRY

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PREFACE

For the past thirty-five years, I have attended nearly all of the biochemistry lectures for the first-year medical students at the four medical schools with which I have been affiliated—first at The Johns Hopkins University School of Medicine, then the University of Colorado School of Medicine, next the College of Medicine and Dentistry of New Jersey, and finally, East Carolina University School of Medicine. The substance of this book is based almost entirely on the content of those lectures. In selecting and arranging the subject material, I have tried to identify the diverse needs of very busy students who are encountering their first and only course in biochemistry.

Serious students of basic and applied biology today have access to many authoritative textbooks and reviews of biochemistry. It would be highly presumptuous to even suggest that this book can substitute for treatises as comprehensive and scholarly as those of Professors Lehninger, White, Handler, Smith, Hill, Lehman, Stryer, Neuhaus, Orten, Mahler, and Cordes. These texts should be in the libraries of all physicians and other advanced students of human biology.

This book is an intermediate-level text. Because it is aimed at a wide audience and is designed for a one-semester course, I have assumed that most students using the text have had minimal exposure to either physical chemistry or organic chemistry. Emphasis has been given to the salient facts of molecular structure and of the organizing principles of chemical behavior that are basic to an understanding of human biochemistry. Such a foundation is essential for all students and practicing professionals in the modern health-related sciences—medicine, dentistry, nursing, and clinical technology.

To bridge the biochemistry of cells, tissues, and organs, the nine units of the book following the initial introductory unit have been grouped into two parts. Part One, "Basic Biochemistry," reviews the vocabulary, elementary concepts, and unifying principles that are important for understanding and describing individual cellular processes. Part One also provides a preview of the principal interrelationships of reaction sequences that are responsible for the synthesis and degradation of the organic compounds of a cell and its environment. Part Two, "Metabolic Basis of Human Biochemistry," presents a perspective of these principles at a higher level of organization and describes the physiologic interdependency of tissues and organs in the integration of metabolic activities in humans. The final portion of this section relates health and disease to states of balance and imbalance in human metabolism. It is hoped that the arrangement of the topics in this manner will accommodate the heterogeneous backgrounds of the readers.

References for additional reading listed at the end of each chapter have been selected to provide the beginning student with a reasonable number of entry points into the biochemical literature.

It is hoped that the problems can assist the students in their efforts at self-examination and provide additional perspectives and illustrations of the subject matter on which they are based.

I am indebted to many colleagues and students for reading, criticizing, and contributing suggestions for parts of the manuscript. Special thanks are due Drs. Sam

Pennington, Richard Marks, Lynis Dohm, Hisham Barakat, George Kasperek, James Fix, Charles Bokelage, Eugene Weinbach, Theodore Peters, and Cosmo Mackenzie, Mr. Kenneth Olive, and Mr. Bruce Henschen. I am indebted to Dr. Marks for his design and supervision of the computer program used in preparing the index. Thanks are also due Inge McMillan for translating the quotation at the beginning of Chapter 4.

I am very grateful to Jane Overman Misslbeck, Patricia Heath, Katrina Searcey, and Sandra Bonzini for their devotion and patience in typing the manuscript. A special word of appreciation is given to Margaret Sullivan for her thoughtful editing and unflagging, enthusiastic attention to the many important details in the final stages of preparation of the book.

I am particularly indebted to the Macmillan Publishing Company for their unfailing courtesy and aid. Ms. Elizabeth Groeneman deserves special acknowledgment for her forbearance and skillful management of the challenges in guiding the book through the final stages of publication. Finally, it is a pleasure to thank Ms. Joan C. Zulch, Vice President of the Company, for her encouragement, unselfish editorial assistance, patience, and friendship.

Wilhelm R. Frisell, Ph.D.

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UNIT I General Considerations

Living organisms contain thousands of both simple and complex molecules, each of which has a function or purpose. The reactions by which these molecules interact with one another and by which they are synthesized and degraded account for the extraordinary attributes of all that is recognized as living. The composition of all of these reactions is a network of branched and interconnected pathways that function as an isothermal, self-replicating, and self-regulating system.

We shall see that even the most complex molecules in an organism are composed of organic building blocks that are relatively simple in kind and few in number. Similarly, the types of reactions that occur in living organisms are reducible to a remarkable simplicity. In this section we categorize the major classes of individual reactions that become linked as metabolic sequences.

CHAPTER 1 ROLE OF BIOCHEMISTRY IN THE HEALTH PROFESSIONS

The properties of living matter can be learned only through their relation to the properties of inorganic matter; it follows that the biological sciences must have as their necessary foundation the physicochemical sciences from which they borrow their means of analysis and their methods of investigation.*

Biochemistry is a science with multiple origins, and its growth has continued to be increasingly interdisciplinary and comprehensive. As it seeks to describe and correlate form and function, biochemistry has become the language of most of the life sciences. Its principles and applications are now a part of the armamentarium of all of the medical sciences, both basic and clinical.

Understandably a student and practitioner of the health-related sciences tends to be preoccupied with "human" biochemistry. Such a label is certainly appropriate when the objective is to describe normal and abnormal biochemical interrelationships at the level of organs and tissues. However, attention must constantly be focused on cells. The cells of human organs and tissues are programmed to make the unique contributions that are recognized as specialized functions and metabolic activities. An understanding of the molecular basis for these distinctive expressions of form and function is a major theme of human biochemistry.

Matching the subtle variations of biochemical patterns that account for specialized functions and individuality of human cells is the remarkable oneness or sameness of these cells. The machinery of one type of cell has much in common with that of another type. Thus, all cells duplicate and transmit genetic information in the same way, use a common mechanism to synthesize protein, transfer energy in a similar manner, and employ comparable means of controlling the overall balance of anabolic and catabolic processes. Even the specialized functions have their origin in phenomena and structures common to all cells. Action potentials, for example, are

* Bernard, Claude: *An Introduction to the Study of Experimental Medicine* (translated by H. C. Greene, 1949), Dover Publications, Inc., New York.

not confined to nerve cells and neither are actomyosin-like protein complexes found exclusively in muscle.

The amazingly rapid advances in biochemistry have been possible because of the revolution of technology of analytical biology in the past two decades. The boundaries between structure and function have merged as we have been able to see smaller and smaller bits of biomolecular architecture and to measure chemical changes over almost vanishingly small time spans. Fifty years ago few glossaries of biology treatises carried definitions of micro-, nano-, pico-, femto-, or atto-. With today's micromethodology, these are commonplace terms even in the clinical laboratories, where applied biochemistry is enjoying unforeseen triumphs. Just as pathologists have moved from the flat, two-dimensional world of the microscopic slide, from which they had to describe lesions in three dimensions, clinical chemists have been able to add the dimension of time to their analytical observations. Consequently, in addition to contributing to a diagnosis by telling clinicians how much of a tissue constituent is present, they have the means to determine both how and how rapidly a substance appears or disappears.

This explosive increase of insights into the molecular machinery of the cell that we have witnessed in the past 20 years has been equaled by an unpredicted rapidity of application of new knowledge to medicine and the other applied life sciences. The increasingly shorter interval of time between discovery and application has been one of the hallmarks of the last half of the twentieth century. The gap (once viewed as unbridgeable) between the properties of individual biomolecules and the integrated activities within whole cells and tissues is now being spanned. A cardinal objective of biochemistry now is to extend our understanding to even higher levels of biological organization that must be dealt with in the science of human medicine. It is timely to recall that 50 years ago Frederick Gowland Hopkins gave focus to this objective when he stated:

> The task of the biochemist wishing to get to the heart of his problem is exceptional in that he must study systems in which the organization of chemical events counts for more, and is carried far beyond, such simpler coordinations as may be found in non-living systems. He would be over-bold were he to claim at present that such high organization can depend alone upon adjusted concentrations and ordered structural distribution among specialized colloidal catalysts; but he is justified, I think, in feeling sure that such factors contribute to that organization in a significant sense. The biochemist when he aims at describing living systems in his own language comes in contact with philosophical thought. Current philosophy is busy in emphasizing the truism that the properties of the whole do not merely summarize but emerge from the properties of its parts; and some exponents hold *a priori* that biochemical data can throw no real light on the nature of an organism which, in its very essence, is a unit. The biologist has long studied living organisms as wholes and will continue to do so with ever-increasing interest. But these studies can tell us nothing of the nature of the "physical basis of life" which no form of philosophy can ignore. It is for chemistry and physics to replace the vague concept "protoplasm"—a pure abstraction—by something more real and descriptive. I know of nothing which has shown that current efforts to this end do not deal with realities. It is only necessary for the biochemist to remember that his data gain their full significance only when he can relate them with the activities of the organism as a whole. He should be bold in experiment but cautious in his claims. His may not be the last word in the description of life, but without his help the last word will never be said.*

* Hopkins, F. G. (1931): *Problems of Specificity in Biochemical Catalysis*, Oxford University Press, Oxford, England.

CHAPTER 2 OVERVIEW OF HUMAN BIOCHEMISTRY

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.*

Chapter Outline

* Berzelius, J. J. (1837): *Lehrbuch der Chemie*, Vol. VI, Leipzig.

SOME OF THE QUESTIONS THAT NEED ANSWERS

In probing relationships between structure and function, the biochemist asks questions such as the following. What chemical compounds are essential for life? What is the nature of the structures of the molecules whose molecular weights are numbered in the hundreds of thousands, the macromolecules, which are characteristic of living organisms? How do enzymes work? How can the materials of the diet, whether it is the diet of an *Escherichia coli* or of a human being, be transformed into compounds characteristic of the cells of a given species? How is the potential energy latent in the foodstuffs of an organism transduced into other energy forms required by the organism? What is the chemistry of inheritance? A related question: How is the genetic information contained in a totipotent, fertilized egg transcribed so as to allow development of a differentiated organism? How are the thousands of different chemical reactions in a cell, each catalyzed by an enzyme, synchronized so that there is harmony between synthesis and breakdown, supply and demand? In an organism as complicated as the human being, how do the specialized cells of tissues and organs make their individualized contributions to our total physiologic economy? How does an organism as compartmentalized as the human being regulate the volume and the composition of the fluids that are his internal environment? When microorganisms, or foreign macromolecules, enter us accidentally, what is the biochemistry of the immune response that will render the invaders harmless? The ultimate question: Can disease be described in molecular terms?

COMPLEXITY, DIVERSITY, AND SIMPLICITY OF BIOMOLECULES AND METABOLIC REACTIONS

A major emphasis in this book is on METABOLISM, the sum of the physical and chemical processes by which living matter is produced and maintained.

Living organisms can be termed OPEN SYSTEMS because they exchange both matter and energy with their environment. That which we call "living" is not in thermodynamic equilibrium with its surroundings. Indeed, it is far removed from equilibrium. Yet when observed over a period of time, an organism apparently does not change—its composition appears to remain constant. If a living system is not in thermodynamic equilibrium, the only alternative for maintaining its state of constancy is to have the rate of transfer of energy and matter into the system precisely balanced by the rate of return of matter and energy to the environment. Accordingly, any consideration of metabolism must take into account both the organism and its environment. The most remarkable aspect of the steady-state condition is that the balance of chemical and physical processes is maintained even in the face of disturbing changes in the environment. It must be concluded, therefore, that the multitudinous processes of metabolism are sensitive to fine control.

Over and above the seemingly countless reactions involved in metabolism, the chemical composition of even the simplest and smallest cells would appear to be hopelessly complicated. Consider a *Pseudomonas* as an example. This bacterium weighs about 2 picograms, or 2×10^{-12} g. In this small, lively package there are about 1000 different kinds of low-molecular-weight organic compounds—10 to 300 million molecules of each. There are also about 3000 different proteins of high molecular weight. The cell has room for about 400 of each of these huge molecules. In addition, there are about 1000 different kinds of nucleic acids and a dozen different

inorganic ions. The rest of the cell's substance, approximately 50 percent, is water. In humans, with our 50 trillion cells, the complexity of biochemical composition is orders of magnitudes greater. In all of the human cells there may be as many as 100,000 different kinds of proteins. The number of different kinds of nucleic acids will also be much greater than in a single-cell organism.

When we consider our entire biosphere, the diversity and numbers and kinds of molecules become even more prodigious. Although the 3000 different kinds of proteins in the bacterium may function the same way as 3000 corresponding protein molecules in humans, none of these molecules in the bacterium is structurally identical with any of the human proteins having the same function. Each species has its own chemically distinct protein and nucleic acid molecules. The approximately 1.5×10^6 species of living organisms in our biosphere contain 10^{10} to 10^{12} different kinds of proteins and 10^{10} different kinds of nucleic acids. The structures of about 10^6 different organic molecules have been determined. Therefore, of all the different organic molecules in all living forms on earth, we know the precise structure of only about 0.0001 percent. In the face of such numbers, how could one think of isolating and identifying all the different organic molecules to be found in living organisms? In addition, if one considers the hundreds of different enzyme-catalyzed reactions in which all of these compounds participate, any comprehensive description of the molecular basis of life appears hopelessly complex. However, the seemingly infinite diversity of organic molecules is reducible to a remarkable simplicity because the number of building-block molecules from which the macromolecules are made are relatively few in number. For example, to make the 100,000 different proteins in humans, only 20 different amino acids are needed. Only eight compounds, called nucleotides, are required to synthesize the thousands of nucleic acids. In addition, these relatively simple building blocks, the amino acids and the nucleotides, can serve other functions in the cell and can become precursors for many other important compounds.

Just as the diversity of kinds of organic molecules in a living organism is more apparent than real, the metabolic pathways involving these molecules also show recurring patterns. The central pathways are in fact very similar in most forms of life—bacteria, soybeans, fish, or humans.

THE CYCLES OF SUBSTANCE AND ENERGY IN OUR BIOSPHERE

In our biosphere, the very thin membrane of life that coats the surface of our planet, there is a cycling of the major elements of the organic substances of life: carbon, oxygen, and nitrogen. As shown in Figure 2–1, living organisms on earth have a symbiotic relationship. They are nutritionally interdependent in that they feed each other. The ultimate source of energy that sustains this syntrophy is the sun. Plants are able to transduce solar energy into chemical energy by a process in which HOH donates electrons to CO_2 to yield carbohydrate and oxygen. Animals, in turn, import the carbohydrate and O_2, transform these fuels into other organic compounds by the process of oxidation, and transduce the energy of oxidation into other forms of biologically useful energy. The end products of these processes in the animal cells are HOH and CO_2, which are returned to the environment to be recycled via the photosynthetic system.

The same nutritional and metabolic interdependency among organisms obtains

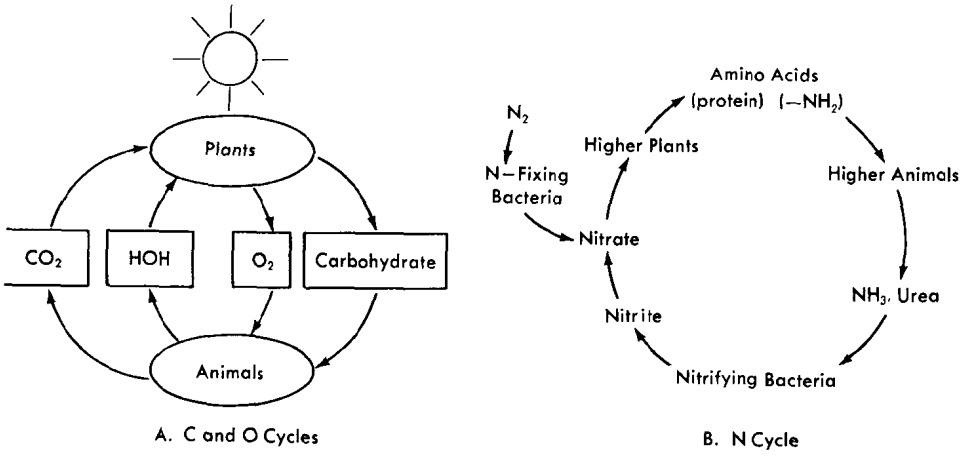

Figure 2-1. The (*A*) C, O, and (*B*) N cycles in the earth's biosphere.

for nitrogen as shown in Figure 2-1*B*. Analogously to the carbon-oxygen cycle, the nitrogen cycle requires a syntrophic relationship among plants, bacteria, and higher animals. Except for the nitrogen-fixing bacteria, most forms of life cannot use molecular nitrogen (N_2), the dominant gas of our atmosphere. Instead, the majority of the earth's organisms obtain their nitrogen as nitrate, NH_3, or amino acids. These three nitrogen forms are the components of the nitrogen cycle in our biosphere.

As pointed out above, the cyclic nature of the conservation of C, N, and O in our biosphere also entails a concurrent transformation of energy. However, in contrast to the reutilization of C, N, and O, the flow of energy is not cyclic but is unidirectional (Figure 2-2). Beginning as light from the sun, energy is transduced into its only useful form for humans—chemical energy (e.g., glucose, ATP, NADPH, etc.). The energy trapped in these compounds can be converted as required into mechanical work, electrical work, transport work, and so on. Energy flow through the biosphere ceases when it is dissipated in the environment as heat and disorder.

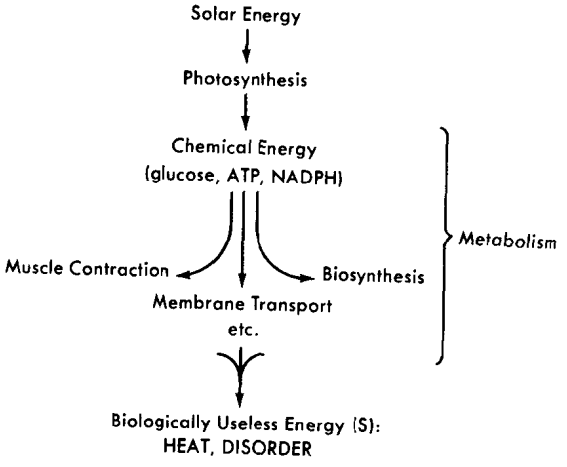

Figure 2-2. Noncyclic nature of energy transformations in our biosphere.

THE INTERDEPENDENCY OF CATABOLIC AND ANABOLIC PROCESSES OF METABOLISM

Metabolism, whether that in yeast cell or in a human being, is the composite of two concurrent processes: degradation or breakdown (catabolism) and building up or biosynthesis (anabolism). Life is possible only when these two processes are linked. The energy as well as many of the molecules generated by the catabolic process are reutilized in anabolism.

The breakdown pathways of human metabolism are convergent, yielding a common intermediate. The oxidation of this compound produces two major end products of metabolism, CO_2 and HOH; and the energy is captured as ATP (Figure 2-3). On the other hand, anabolism has a pattern of divergent pathways. Starting from relatively few and simple precursors, the biosynthetic pathways result in many different kinds of molecules (e.g., glucose, proteins, lipids, nucleic acids, etc.). However, no matter by which of these divergent pathways synthesis occurs, the price of anabolism is chemical energy, the energy generated in the catabolic pathways.

The "gears" that link catabolism and energy-requiring processes are phosphate and electrons. As shown in Figure 2-4*A*, the energy made available by oxidation of foodstuffs is used to synthesize ATP from ADP and phosphate. The ATP in turn

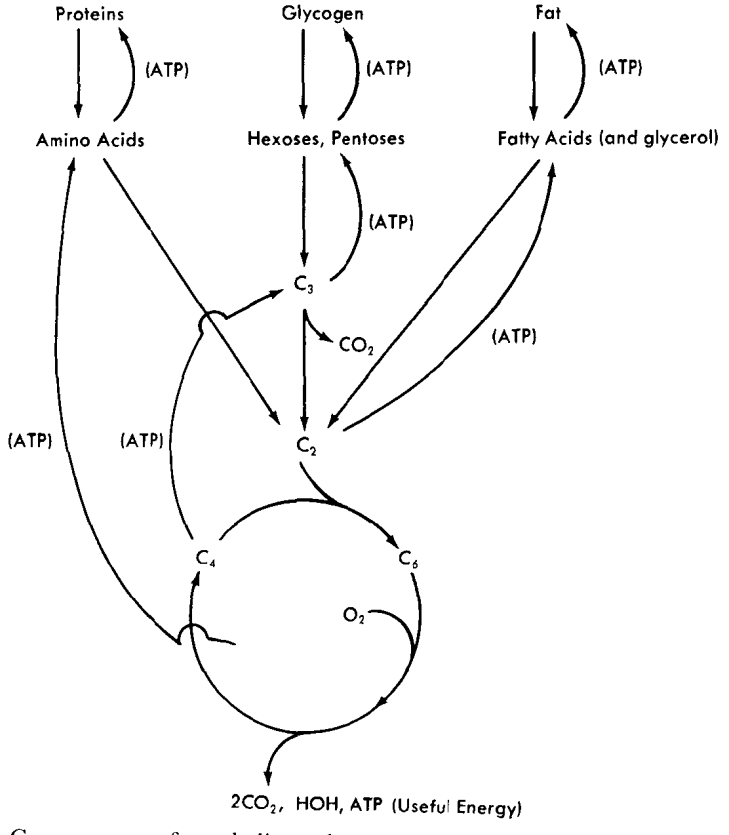

Figure 2-3. Convergence of catabolic pathways and divergence of anabolic pathways in metabolism.

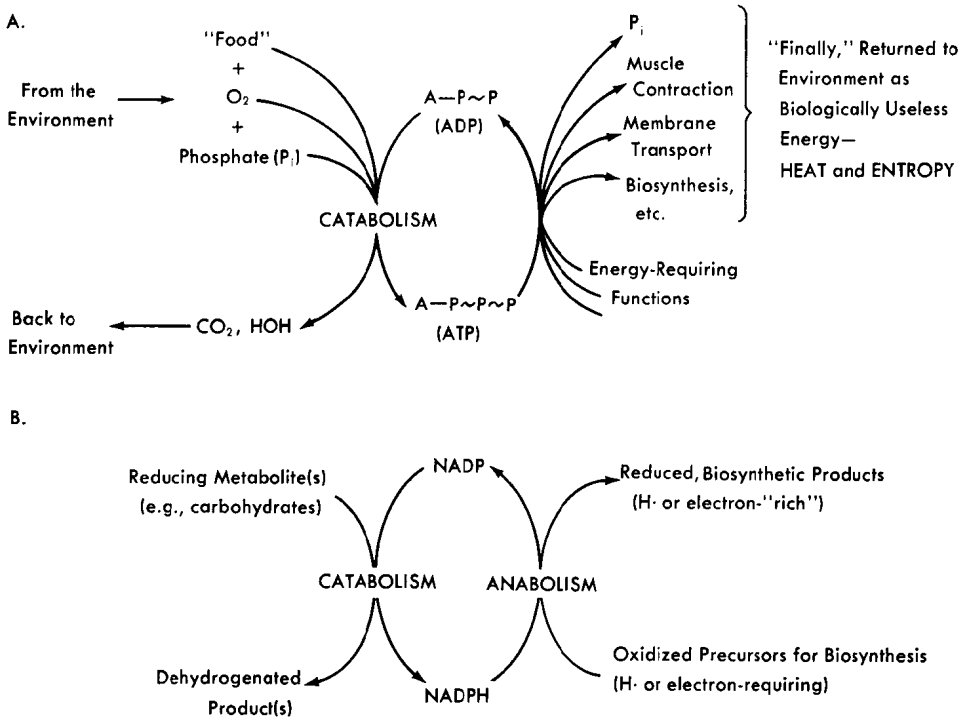

Figure 2-4. *A.* The "phosphate cycle." *B.* Electron transfer from catabolic to anabolic processes.

becomes the common currency for the energy exchange involved in such functionally different processes as muscle contraction, transport of substances across membranes, biosynthesis, and so on. As its energy is transduced, the ATP is broken down to ADP and phosphate. The cycling of phosphate can continue as long as additional food molecules and O_2 are entering the system.

Many biosynthetic reactions in animal cells require the addition of electrons or hydrogen atoms to precursor molecules. The most common carrier of the electrons or hydrogen atoms for such reductive processes is a derivative of the vitamin niacin, NADP (Chapter 6) as shown in Figure 2-4*B*. Just as ATP carries high-energy phosphate, NADP in its reduced form of NADPH can be considered to provide energy-rich electrons for biosynthesis.

The phosphate and electron transfer cycles illustrate how the free energy of cellular fuels is conserved and made available for energy-requiring processes. This exchange of chemical energy in a living cell occurs isothermally (i.e., at one temperature), in contrast to a machine, whose operation depends on the flow of heat from one part to another part of a lower temperature.

THE DYNAMIC STEADY STATE OF HUMAN METABOLISM

To gain another view of the molecular basis of the processes involving exchange of both matter and energy in living systems, let us now turn to a more macroscopic and familiar aspect of human metabolism. We have said that the human being is no different from every other living organism, being an open system constantly ex-