Seek simplicity and distrust it.

Alfred North Whitehead

Preface

The ballooning of biochemistry texts in the past couple of decades inspired us to follow Whitehead's imperative. This is a short book—less than 700 text pages—in territory dominated by giant tomes.

Probably most teachers, certainly most students, would prefer a shorter text, but the ideal edition would have to be tailored to fit the array of topics and emphases each teacher prefers. So, perversely, the wish for brevity engenders increasingly fatter volumes as publishers encourage authors to write encyclopedic texts in hopes that teachers will carve from this bulk a diversity of shapes, each one suited to a particular course.

The "one-size-fits-all" strategy seems to be adaptive—megatexts abound. But there is a cost to those who must use them. Students can get lost in thickets of detail and fail to capture essential principles. It is this dilemma that motivated our effort to "seek simplicity" by focusing on principles while remaining ever mindful of the second part of Whitehead's advice.

This book is intended to serve teachers and students engaged in full-year courses as well as short ones. We treat basic processes with a depth comparable to that achieved by much longer texts. Our coverage of biomolecules, enzymes, energetics, and metabolism is substantial enough to suit standard introductory courses, whatever their length. Only elaborations and tangential excursions have been set aside. Our story of biological information flow is told in three chapters, enough molecular biology for the beginning biochemistry student since this elegant subject receives detailed treatment in subsequent courses.

We count on students having behind them introductory courses in general and organic chemistry, and we build a solid chemical foundation by elucidating reaction mechanisms where these will improve understanding without confusing or discouraging our readers. The physiologically important forms of ionizable groups are shown consistently, and stereochemically correct structures are emphasized where they are important. Computer-generated stereo views (many developed especially for this text by Jane and David Richardson's group at Duke University) clarify the shape and function of biomolecules. A stereoviewer comes with each copy of the text.

The narrative is up-to-date. There are a number of new descriptions of three-dimensional protein structures based on recent X-ray crystallographic work. We also include, to name a few examples, new information on the role of chaperones in protein folding, new molecular data revealing evolutionary relationships among organisms, new work on the role of transition-state stabilization in enzyme catalysis and on transition-state analogs and the generation of catalytic antibodies, newly identified prosthetic groups, the role of histidine in the activity of triose phosphate isomerase, new images of DNA visualized by scanning tunnelling electron microscopy, new insights into the energetics and regulation of metabolism, new work on the Q cycle in oxidative phosphorylation and photophosphorylation, new research on the formation of spliceosome complexes and their role in RNA processing, and new information on the structure and function of ribosomes.

The text also offers significant innovations in the teaching of broad principles, revealing unity and pattern within the details. The chapter on enzyme mechanisms and the following one on coenzymes categorize the major types of reaction mechanisms students will encounter in their study of metabolism later in the book. These mechanisms, when they appear within metabolic pathways, can then be welcomed as familiar roadmarks rather than endured as unfamiliar detours.

Coenzymes are treated as a central feature of pathways rather than simply as side-products of reactions. The distinction between mobile cosubstrates and bound prosthetic groups is clearly drawn in the chapter on coenzymes and reinforced throughout the metabolism chapters. In particular, the role of FAD is clarified. Many books show reduced FAD as a coproduct of reactions, suggesting a parallelism between it and mobile cosubstrates such as NAD and ubiquinone (Q). Our text emphasizes that FAD, as an enzyme-bound prosthetic group, is not released to solvent but must be converted back to its oxidized form with each catalytic cycle by donating its electrons (and protons) to a mobile cosubstrate such as Q. We identify the mobile carrier, rather than FAD, as the product in such reactions. Q, often introduced only within the context of the respiratory electron-transport chain, is introduced in this text in the chapter on coenzymes. It appears as a mobile cosubstrate of the succinate dehydrogenase complex in the citric acid cycle and is a familiar player by the time students learn of its role in oxidative phosphorylation.

The chapter on bioenergetics clearly delineates the difference between standard and actual changes in free energy and explains why standard values cannot be used as predictors of the direction of metabolic flux in vivo. We explain that the actual change in free energy in the metabolic steady state indicates whether a reaction is near equilibrium or metabolically irreversible and that only metabolically irreversible reactions are subject to regulation. We emphasize biochemical events in vivo and contrast them with experimental observations in vitro that have led to misconceptions about certain physiological processes. In this chapter, we also make clear the connection between reduction potential and free-energy change, thus giving students an overview of the primary energy transactions prior to discussing details of metabolic pathways. Many texts explain reduction potential only within the chapter on oxidative phosphorylation, thereby delaying (if not preventing) an understanding of energy flux between catabolic and biosynthetic processes.

Our chapter on oxidative phosphorylation is unique among current texts in developing an understanding of chemiosmosis *before* describing the details of electron transport coupled to the synthesis of ATP. An insightful comparison of protonmotive force to electromotive force gives the student an immediate understanding of the energy that drives oxidative phosphorylation.

Principles of Biochemistry has four parts. Part One contains two chapters that introduce the subject. In Chapter 1, we review fundamental aspects of cell structure and function and give an overview of biomolecular structures, touching upon historical landmarks in the development of biochemistry and molecular biology. In Chapter 2, we consider the properties of water, introducing its role in solution chemistry, its ionization, and its contribution to the stability and reactivity of biomolecules and macromolecular assemblies.

Part Two contains eight chapters on the structures of biomolecules and the relationship of molecular architecture and chemical reactivity to biological function. We first examine amino acids, their structures, ionic properties, reactivities, and linkages within proteins (Chapter 3); this discussion serves as background for the next topic—the three-dimensional structures of proteins in relation to their physiological functions (Chapter 4). In the next three chapters, we examine the fundamental principles of enzyme catalysis: the general properties and classification of enzymes, enzyme kinetics, and allosteric transitions (Chapter 5); mechanisms of enzymatic catalysis and the roles of amino acid residues within active sites, as both chemical reactants and binding sites (Chapter 6); and the involvement of coenzymes as cosubstrates and prosthetic groups within the active sites of enzymes (Chapter 7). We continue Part Two by examining the structure and function of three other major classes of biomolecules: carbohydrates (Chapter 8); lipids and biological membranes (Chapter 9), which includes a discussion of membrane transport; and nucleic acids (Chapter 10).

Part Three contains nine chapters dealing with bioenergetics and transformations of biomolecules. In Chapter 11, we give an overview of metabolism and guide the student through thermodynamic principles that underlie bioenergetics, emphasizing the roles of energy-rich metabolites, such as ATP, and reduced coenzymes, such as NADH. We next describe glycolysis (Chapter 12) and introduce hormone action and second messengers; then we cover the citric acid cycle, describing its central role in aerobic metabolism (Chapter 13), and follow with an explanation of oxidative phosphorylation (Chapter 14). Glycogen metabolism, gluconeogenesis, and the pentose phosphate pathway come next (Chapter 15), followed by a modern view of photosynthesis (Chapter 16), metabolism of fatty acids (Chapter 17), metabolism of amino acids (Chapter 18), and metabolism of purine and pyrimidine nucleotides, the biochemical precursors of nucleic acids (Chapter 19).

Part Four concludes the book with three chapters on the flow of biological information; in these chapters, we sustain our emphasis on central principles, covering recent discoveries and showing the chemical mechanisms underlying the molecular biology of gene expression and its regulation. In Chapter 20, we describe replication and repair of DNA, followed by transcription and the processing of RNA (Chapter 21), and protein synthesis (Chapter 22).

Science is more and more a collaborative effort, several workers joining forces in one and sometimes two or more laboratories. Science textbook publishing is likewise an increasingly collăborative enterprise. There still are estimable texts by single authors, but the trend is toward sharing the work. Each author of this text wrote chapters in his particular area of expertise but also collaborated with the other authors and the publishing group to ensure a unified presentation. A brief biographical account of the authors is given on page v; the identity of each player on the publishing side—editors, artists, and the like—is shown on page vi; and the invaluable reviewers and advisors who helped guide this project are listed on pages x and xi.

Whoever said "I wrote a long letter because I didn't have time to write a short one" nicely caught the irony of our experience in producing *Principles of Biochemistry*. It took us more than a sensible amount of time and labor to draw from this burgeoning science the core of ideas and processes that a first course in biochemistry must offer in these days of ferment and discovery.

Neil Patterson

Chapel Hill

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