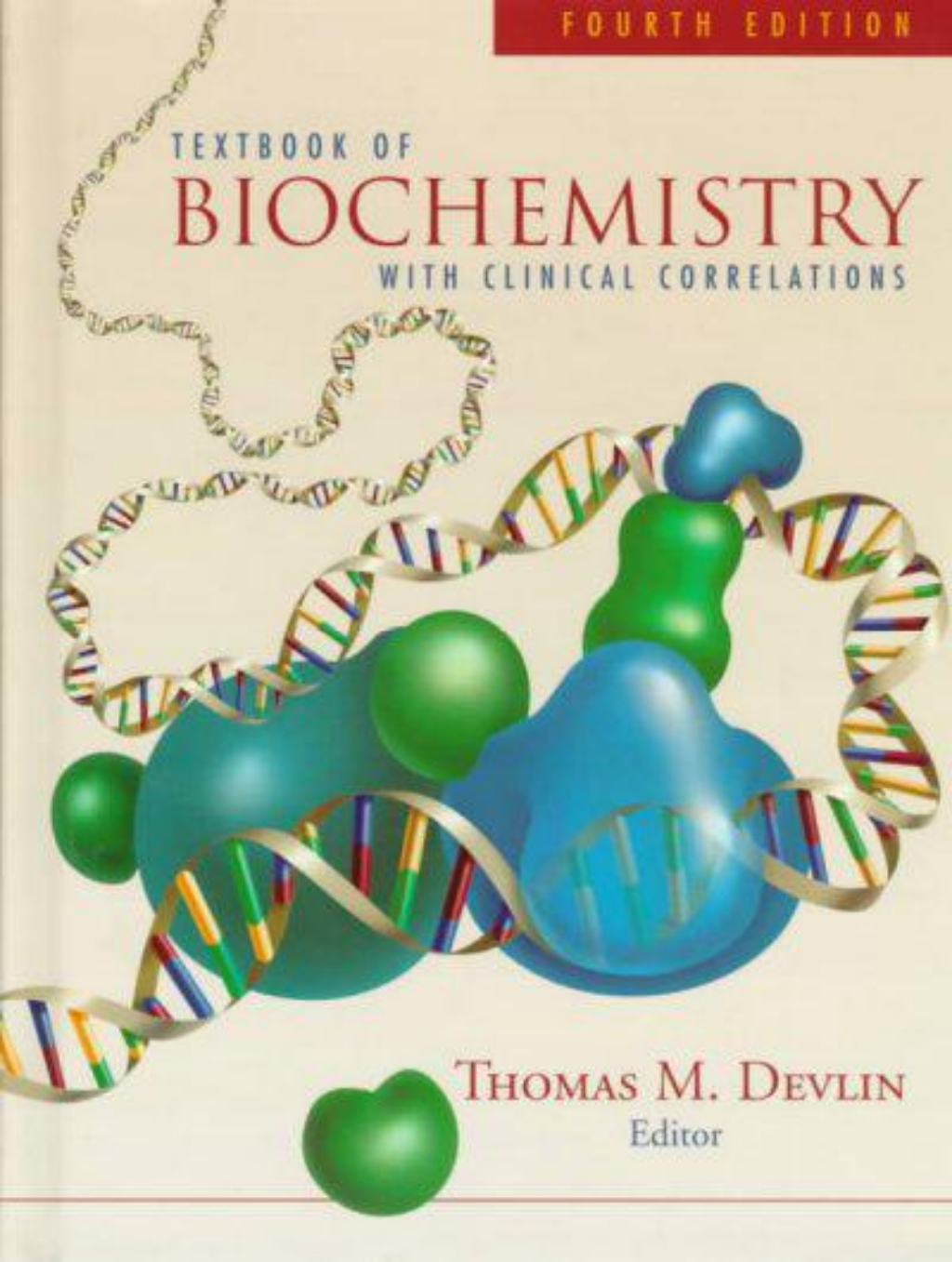


FOURTH EDITION

TEXTBOOK OF

# BIOCHEMISTRY

WITH CLINICAL CORRELATIONS



THOMAS M. DEVLIN

Editor

# **Textbook of Biochemistry with Clinical Correlations**

Fourth Edition

## Abbreviations in Biochemistry

<b>A (or Ade)</b>	adenine
<b>ACP</b>	acyl carrier protein
<b>ACTH</b>	adrenocorticotrophic hormone
<b>acyl coA</b>	acyl derivative of CoA
<b>ADH</b>	antidiuretic hormone
<b>AdoMet</b>	adenosylmethionine
<b>Ala</b>	alanine
<b>ALA</b>	aminolevulinic acid
<b>AMP</b>	adenosine monophosphate
<b>cAMP</b>	cyclic AMP
<b>Arg</b>	arginine
<b>Asn</b>	asparagine
<b>Asp</b>	aspartate
<b>ATP</b>	adenosine triphosphate
<b>ATPase</b>	adenosine triphosphatase
<b>BMR</b>	basal metabolic rate
<b>BPG</b>	D-2,3 bisphosphoglycerate
<b>C (or Cyt)</b>	cytosine
<b>CDP</b>	cytidine diphosphate
<b>CMP</b>	cytidine monophosphate
<b>CTP</b>	cytidine triphosphate
<b>CoA or CoASH</b>	coenzyme A
<b>CoQ</b>	coenzyme Q (ubiquinone)
<b>cyclic AMP</b>	adenosine 3',5'-cyclic monophosphate
<b>cyclic GMP</b>	guanosine 3',5'-cyclic monophosphate
<b>Cys</b>	cysteine
<b>d</b>	2'-deoxyribo
<b>DNA</b>	deoxyribonucleic acid
<b>cDNA</b>	complementary DNA
<b>dopa</b>	3,4-dihydroxyphenylalanine
<b>EcoRI</b>	EcoRI restriction endonuclease
<b>FAD</b>	flavin adenine dinucleotide (oxidized form)
<b>FADH<sub>2</sub></b>	flavin adenine dinucleotide (reduced form)
<b>fMet</b>	formylmethionine
<b>FMN</b>	flavin mononucleotide (oxidized form)
<b>FMNH<sub>2</sub></b>	flavin mononucleotide (reduced form)
<b>Fp</b>	flavoprotein
<b>G (or Gua)</b>	guanine
<b>GABA</b>	$\gamma$ -aminobutyric acid
<b>Gal</b>	galactose
<b>Glc</b>	glucose
<b>Gln</b>	glutamine
<b>Glu</b>	glutamate
<b>Gly</b>	glycine
<b>GDP</b>	guanosine diphosphate
<b>GMP</b>	guanosine monophosphate
<b>GTP</b>	guanosine triphosphate
<b>GSH</b>	glutathione
<b>Hb</b>	hemoglobin
<b>HbCO</b>	carbon monoxide hemoglobin
<b>HbO<sub>2</sub></b>	oxyhemoglobin
<b>HDL</b>	high density lipoprotein
<b>HMG CoA</b>	$\beta$ -hydroxy- $\beta$ -methylglutaryl CoA
<b>Hyp</b>	hydroxyproline
<b>IDL</b>	intermediate density lipoprotein
<b>IgG</b>	immunoglobulin G
<b>Ile</b>	isoleucine
<b>IP<sub>3</sub></b>	inositol 1,4,5 trisphosphate
<b>ITP</b>	inosine triphosphate
<b>K<sub>m</sub></b>	Michaelis–Menten constant
<b>kb</b>	kilo base pair
<b>LDL</b>	low density lipoprotein
<b>Leu</b>	leucine
<b>Lys</b>	lysine
<b>Mb</b>	myoglobin
<b>MbO<sub>2</sub></b>	oxymyoglobin
<b>Met</b>	methionine
<b>MetHb</b>	methemoglobin
<b>NAD<sup>+</sup></b>	nicotinamide adenine dinucleotide (oxidized form)
<b>NADH</b>	nicotinamide adenine dinucleotide (reduced form)
<b>NADP<sup>+</sup></b>	nicotinamide adenine dinucleotide phosphate (oxidized form)
<b>NADPH</b>	nicotinamide adenine dinucleotide phosphate (reduced form)
<b>NANA</b>	N-acetylneuraminic acid
<b>PEP</b>	phosphoenolpyruvate
<b>Phe</b>	phenylalanine
<b>P<sub>i</sub></b>	inorganic orthophosphate
<b>PG</b>	prostaglandin
<b>PP<sub>i</sub></b>	inorganic pyrophosphate
<b>Pro</b>	proline
<b>PRPP</b>	phosphoribosylpyrophosphate
<b>Q</b>	ubiquinone (CoQ)
<b>RNA</b>	ribonucleic acid
<b>mRNA</b>	messenger RNA
<b>rRNA</b>	ribosomal RNA
<b>tRNA</b>	transfer RNA
<b>RNase</b>	ribonuclease
<b>RQ</b>	respiratory quotient (CO <sub>2</sub> production/O <sub>2</sub> consumption)
<b>S</b>	Svedberg unit
<b>SAM</b>	S-adenosylmethionine
<b>Ser</b>	serine
<b>SH</b>	sulfhydryl
<b>T (or Thy)</b>	thymine
<b>TCA</b>	Tricarboxylic acid cycle (Krebs cycle)
<b>TG</b>	triacylglycerol
<b>THF</b>	tetrahydrofolic acid
<b>Thr</b>	threonine
<b>TPP</b>	thiamine pyrophosphate
<b>Trp</b>	tryptophan
<b>TTP</b>	thymidine triphosphate
<b>Tyr</b>	tyrosine
<b>U (or Ura)</b>	uracil
<b>UDP</b>	uridine diphosphate
<b>UDP-galactose</b>	uridine diphosphate galactose
<b>UDP-glucose</b>	uridine diphosphate glucose
<b>UMP</b>	uridine monophosphate
<b>UTP</b>	uridine triphosphate
<b>Val</b>	valine
<b>VLDL</b>	very low density lipoprotein

**Textbook of Biochemistry with Clinical Correlations:  
Fourth Edition**

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*To  
Katie, Matthew, Ryan, and Laura*

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## Foreword

These are very exciting times for biochemistry and especially for that part that pertains to human biology and human medicine. The much discussed Human Genome Project is likely to be completed very early in the next millennium, by the time most users of *Textbook of Biochemistry With Clinical Correlations* have graduated. The Human Genome Project should provide a blueprint of the 100,000 or so genes that the human genome is estimated to contain and lead to an explosion of amazing proportions in knowledge on complex physiological processes and multigenic disorders. This mapping will reveal undreamed of interrelationships and elucidate control mechanisms of the fundamental processes of development of the human organism and of their interactions with both milieus (the internal and external). Already, one eukaryotic genome (that of brewer's yeast, comprising 14 million base pairs in 16 chromosomes) was completed just before I set out to write this Foreword, while three microbial genomes (that of *Mycoplasma genitalium*—580,070 base pairs, *Hemophilus influenzae*—1.83 million base pairs, and *Synechosystis*—a photosynthetic organism—3.57 million base pairs) have been completed within 3 to 18 months of isolation of their DNA. Work on the genomes of *Mycobacterium tuberculosis* (4.5 million base pairs) and of *Plasmodium falciparum*—the malarial parasite (27 million base pairs in 14 chromosomes)—is now being undertaken and should lead to knowledge that can produce novel approaches to the treatment and control of these two scourges of humankind. The theoretical and technical principles involved in this type of work are clearly described in Chapters 14, 15, and 18 of *Textbook of Biochemistry With Clinical Correlations*, which will ensure that readers will understand and appreciate future developments in the field.

Discoveries on the molecular basis of human disease are also being reported at an unprecedented and dizzying rate, opening wider and wider the window to many less frequent afflictions produced by mutated genes accumulating in the human gene pool. The era of molecular medicine has already arrived. Since the very first edition of *Textbook of Biochemistry With Clinical Correlations*, the correlations have been a feature that has made the book truly unique. In this new edition, the correlations are numerous, succinct, and integrated with, but also independent of, the text. They not only reflect current progress but indicate more than ever before how biochemistry, molecular biology, and human genetics have become the foundation stones of all areas of modern medicine. These previously separate disciplines have become so intimately and inextricably intertwined that little knowledge and understanding of one can occur without knowledge and understanding of others. One of the many strengths of this book is that clear examples of the convergence and integration of biological disciplines can be found in the clinical correlations.

In this fourth edition of *Textbook of Biochemistry With Clinical Correlations*, the contributors have provided an up-to-date and logical coverage of basic biochemistry, molecular biology, and normal and abnormal aspects of physiological chemistry. This material is appropriate and relevant for medical and other health science students, particularly as we approach the third millenium in the midst of amazing and pervasive progress in medical science and biotechnology. To enhance the text, a completely new series of vivid illustrations has been added, which will undoubtedly further the readers' understanding of the complexity of many of the concepts. Students of medical and health sciences should appreciate that the time and effort invested in learning the material presented here will be very well spent. This knowledge will provide the framework within which further developments will be understood and applied as the readers begin to care for the physical and mental well-being of those entrusted to them. Furthermore, the knowledge derived from this book will also provide satisfying insight into the processes that underlie human life and the amazing power of the human mind to explore and understand it. As in previous editions, the fourth edition includes many multiple choice questions (and answers) at the end of each chapter that should facilitate this learning while ensuring success in professional and other examinations.

I am happy and privileged to have watched the growth of human biochemistry (because of my teaching and research responsibilities) since my medical student days nearly half-a-century ago. It has been an amazing spectacle, full of thrills and exciting adventures into aspects of human cells that were previously shrouded in mystery and ignorance. As my knowledge has increased, so has my sense of awe and wonder at the unfolding beauty of this marvelous display of nature's secrets.

As the late Alberto Sols frequently said: "The Biochemistry of today is the Medicine of tomorrow." *Textbook of Biochemistry With Clinical Correlations* illustrates the veracity of this insight.

FRANK VELLA  
UNIVERSITY OF SASKATCHEWAN

## Preface

The purposes of the fourth edition of the *Textbook of Biochemistry With Clinical Correlations* remain unchanged from the earlier editions: to present a clear discussion of the biochemistry of mammalian cells; to relate the biochemical events at the cellular level to the physiological processes occurring in the whole animal; and to cite examples of deviant biochemical processes in human disease.

The continued rapid advances in knowledge, particularly due to the techniques of molecular biology, required a critical review and evaluation of the entire content of the previous edition. Every chapter has been revised and updated. Significant additions of new material, clarifications, and some deletions were made throughout. Amino acid metabolism was combined into a single chapter and DNA structure and function was divided into two chapters for better coverage of this rapidly expanding field. Topics for inclusion were selected to cover the essential areas of both biochemistry and physiological chemistry for upper-level undergraduate, graduate-level and especially professional school courses in biochemistry. Since the application of biochemistry is so important to human medicine, the text has an overriding emphasis on the biochemistry of mammalian cells.

The textbook is written such that any sequence considered most appropriate by an instructor can be presented. It is not formally divided into major sections, but related topics are grouped together. After an introductory chapter on cell structure, Chapters 2 to 5 concern the **Major Structural Components of Cells**, that is, proteins and their many functions, and cell membranes and their major roles. **Metabolism** is discussed in the following eight chapters, starting with the conservation of energy, then the synthesis and degradation of the major cellular components, and concluding with a chapter on the integration of these pathways in humans. The next section of six chapters covers **Information Transfer and Its Control**, describing the structure and synthesis of the major cellular macromolecules, that is, DNA, RNA, and protein. A separate chapter on **Biotechnology** is included because information from this area has had such a significant impact on the development of our current state of biochemical knowledge. The section concludes with a chapter on the **Regulation of Gene Expression** in which mechanisms in both prokaryotes and eukaryotes are presented. The fourth major section represents **Signal Transduction and Amplification** and includes two chapters on hormones that emphasize their biochemical functions as messengers and a chapter on **Molecular Cell Biology** describes four major mammalian signal transducing systems. The textbook concludes with six chapters on topics that comprise **Physiological Chemistry**, including cytochrome P450 enzymes and xenobiotic metabolism, iron and heme metabolism, gas transport and pH regulation, digestion and absorption, and human nutrition.

A major addition from previous editions is the extensive use of color in the **illustrations** as a means to emphasize important points. All figures were reviewed and new drawings were prepared to illustrate the narrative discussion. In many cases the adage "A picture is worth a thousand words" is appropriate and the reader is encouraged to study the illustrations because they are meant to illuminate often confusing aspects of a topic.

In each chapter the relevancy of the topic to human life processes are presented in **Clinical Correlations**, which describe the aberrant biochemistry of disease states. A number of new correlations have been included. The correlations are not intended to review all of the major diseases but rather to cite examples of disease processes where the biochemical implications are well established. In addition, we specifically avoided presenting clinical case reports because it was considered more significant to deal with the general clinical condition. References are included to facilitate exploration of the topic in more detail. In some cases similar clinical problems are presented in different chapters, but each from a different perspective. All pertinent biochemical information is presented in the main text, and an understanding of the material does not require a reading of the correlations. In a few cases, clinical discussions are part of the principal text because of the close relationship of some topics to medical conditions.

Each chapter concludes with a set of **Questions and Answers**; the multiple-choice format was retained as being valuable to students for self-assessment of their knowledge. The question type was limited to the types now occurring in national examinations. All questions were reviewed and many new ones added. The questions cover a range of topics in each chapter, and each has an annotated answer, with references to the page in the textbook covering the content of the question.

The appendix, **Review of Organic Chemistry**, is designed as a ready reference for the nomenclature and structures of organic molecules encountered in biochemistry and is not intended as a comprehensive review of organic chemistry. The material is presented in the Appendix rather than at the beginning of those chapters dealing with the metabolism of each class of organic molecules. The reader might find it

valuable to become familiar with the content and then use the Appendix as a ready reference when reading related sections in the main text.

We still believe that a multicontributor textbook is the best approach to achieve an accurate and current presentation of biochemistry. Each author is involved actively in teaching biochemistry in a medical or graduate school and has an active research interest in the field in which he or she has written. Thus, each has the perspective of the classroom instructor, with the experience to select the topics and determine the emphasis required for students in a course of biochemistry. Every contributor, however, brings to the book an individual approach, leading to some differences in presentation. However, every chapter was critically edited and revised in order to have a consistent writing style and to eliminate repetitions and redundancies. A limited repetition of some topics in different chapters was permitted when it was considered that the repetition would facilitate the learning process.

The individual contributors were requested to prepare their chapters for a **teaching book**. The book is not intended as a compendium of biochemical facts or a review of the current literature, but each chapter contains sufficient detail on the subject to make it useful as a resource. Each contributor was requested not to refer to specific researchers; our apologies to those many biochemists who rightfully should be acknowledged for their outstanding research contributions to the field of biochemistry. Each chapter contains a **Bibliography** that can be used as an entry point to the research literature.

In any project one person must accept the responsibility for the final product. The decisions concerning the selection of topics and format, reviewing the drafts, and responsibility for the final checking of the book were entirely mine. I welcome comments, criticisms, and suggestions from the students, faculty, and professionals who use this textbook. It is our hope that this work will be of value to those embarking on the exciting experience of learning biochemistry for the first time and to those who are returning to a topic in which the information is expanding so rapidly.

THOMAS M. DEVLIN

## Acknowledgments

Without the encouragement and participation of many people, this project would never have been accomplished. My personal and very deep appreciation goes to each of the contributors for accepting the challenge of preparing the chapters, for sharing their ideas and making recommendations to improve the book, for accepting so readily suggestions to modify their contributions, and for cooperating throughout the period of preparation. To each I extend my sincerest thanks for a job well done.

The contributors received the support of associates and students in the preparation of their chapters, and, for fear of omitting someone, it was decided not to acknowledge individuals by name. To everyone who gave time unselfishly and shared in the objective and critical evaluation of the text, we extend a sincere thank you. In addition, every contributor has been influenced by former teachers and colleagues, various reference resources, and, of course, the research literature of biochemistry; we are deeply indebted to these many sources of inspiration.

I am particularly indebted to Dr. Frank Vella, Professor of Biochemistry at the University of Saskatchewan, Canada, who assisted me in editing the text. Dr. Vella is a distinguished biochemist who has made a major personal effort to improve the teaching of biochemistry throughout the world. He read every chapter in draft form and made significant suggestions for clarifying and improving the presentation. Dr. Vella also honored me by writing the Foreword to the fourth edition of this textbook. I extend to him my deepest appreciation and thanks for his participation and friendship.

A very special thanks to two friends and colleagues who again have been of immeasurable value to me during the preparation of this edition: My gratitude goes to Dr. James Baggott, who patiently allowed me to use him as a sounding board for ideas and who unselfishly shared with me his suggestions and criticisms of the text, and to Dr. Carol Angstadt, who reviewed many of the chapters and gave me valuable suggestions. To each I extend my deepest gratitude.

I extend my sincerest appreciation and thanks to the members of the staff of the STM Division of John Wiley & Sons who participated in the preparation of this edition. Special recognition and thanks go to Dr. Brian Crawford, Vice President and General Manager of Life Sciences and Medicine, who gave his unqualified support to the preparation of the fourth edition. I am indebted to Joe Ingram, Publisher, Life Sciences, who conscientiously guided the planning of this edition. I am very indebted to Dr. Stephanie Diment, Associate Editor, for always being available to answer questions and to make valuable suggestions, and who has patiently kept me on track. She has been a constant support; thank you. My deepest appreciation is extended to John Sollami, Senior Managing Editor, who with constant good humor meticulously oversaw the production. He kept the flow of activities reasonable, listened patiently to my suggestions and concerns, and kept us on schedule. It has been a real pleasure to work with a really knowledgeable and conscientious professional and to him I extend a very special thanks. I extend to Louise Page, New Media Editor, my deepest appreciation for her skillful organization of the CD containing the figures from the textbook. Credit for the design of the book goes to Laura Ierardi, to whom I extend my appreciation. My thanks to Christina Della Bartolomea, copyeditor, and Maria Coughlin, indexer, both of whom did an excellent job. A significant improvement in this edition is the addition of many original illustrations. My most heartfelt thanks go to Dean Gonzalez, STM Illustration Manager, and Barbara Kennedy, Illustration Supervisor, at Wiley, who handled the details and flow of illustrations. A special recognition is extended to Dr. Lisa Gardner, Production Manager and Editor of Page Two, and her staff who transformed the rough drawings of the contributors into meaningful illustrations. No book is successful without the activities of a Marketing Department; special thanks are due to Reed Elfenbein, Vice President, Marketing and Sales, David Stier, Senior Marketing Manager, David Steltenkamp, Associate Marketing Manager, and their colleagues at Wiley for their new ideas and efforts.

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## Chapter Questions and Answers

The questions at the end of each chapter are provided to help you test your knowledge and increase your understanding of biochemistry. Since they are intended to help you strengthen your knowledge, their construction does not always conform to principles for assessing your retention of individual facts. Specifically, you will sometimes be expected to draw on your knowledge of several areas to answer a single question, and some questions may take longer to analyze than the average time allowed on certain national examinations. Occasionally, you may disagree with the answer. If this occurs, we hope that after you read the commentary that accompanies the answer to the question, you will see the point and your insight into the biochemical problem will be increased.

The question types conform to those currently used in objective examinations. They are:

Type 1: Choose the one best answer

Type 2: Match the numbered statement or phrase with one of the lettered options given above.