EIGHTH **edition**

Clinical Chemistry

Principles, Techniques, and Correlations

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Principles, Techniques, and Correlations

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In memory of my mother, *Betty Beck Bishop*, *for her constant support, guidance, and*

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MLB

To Nancy, my wife, for continuing support and dedication.

EPF

To my wife, Anita, for continuing support.

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foreword to the eighth edition

For many years, the health care and medical laboratory communities have been preparing for an impending workforce shortage that could threaten to compromise patient care and safety. It is vital that the medical laboratory community continue to educate and prepare credentialed professionals who can work efficiently, have essential analytical and critical thinking skills, and can communicate test results and test needs to health care providers. While the shortage of qualified laboratory practitioners has been in the forefront of our collective thoughts, a more insidious shortage has also arisen among the ranks of faculty within medical laboratory education programs.

As a profession, we have long been blessed with dedicated faculty who strive to impart their knowledge and experience onto countless students. We know, however, that many of these dedicated faculty members have and will continue to step aside to pursue other passions through retirement. As new dedicated faculty step up to take over, we must support these new educators in their roles as program directors and content specialists. Furthermore, we must provide tools for these educators about techniques and theories that are appropriate as they continue to develop their curricula.

One potential tool to assist educators is the American Society for Clinical Laboratory Science (ASCLS) Entry Level Curriculum. At the 2016 ASCLS Annual Meeting, the House of Delegates adopted a newly formatted version of the entry level curriculum for MLT and MLS programs. This document had not been updated since 2002, and a subcommittee of the ASCLS Education Scientific Assembly was charged with editing the document to better represent the field's expectations of new graduates. Subcommittee members solicited feedback from educators and professionals in all subdisciplines and reviewed the content for currency. New material was added to reflect techniques and theories that have emerged since the last edition while material was removed if it was no longer deemed relevant. After this extensive process, the final document is reflective of what the industry demands of a new professional.

Similarly, the material presented throughout *Clinical Chemistry: Principles, Techniques, and Correlations* has always kept current with changes in the laboratory industry. This exceptional ability of authors and editors to keep pace with the needs of an ever-changing profession has not diminished through its, now, eight editions. The content inherent to the discipline of clinical chemistry is foundational to all other areas of laboratory medicine. The eighth edition of this textbook is ideal for students learning the principles of clinical chemistry while helping them build connections to other areas of the laboratory. The chapters have a perfect blend of basic theory and practical information that allows the student to comprehend each area of clinical chemistry. The text is well organized to help MLT and MLS educators distinguish what each unique student population needs to be successful in the marketplace. The online materials, powerpoints, and exam questions, for educators, are an invaluable resource for those creating a new course or revising a current course.

As we face this transition of laboratory practitioners who perform testing and faculty who train and educate our students, products that stay current with the times and help facilitate better understanding of the unique levels of practice within our field are the most essential element to success. The eighth edition of *Clinical Chemistry: Principles, Techniques, and Correlations* accomplishes this and serves as an invaluable tool for any new educator looking for guidance, or seasoned educator looking to refresh their teachings.

As educators we are thrilled that students continue to find the field of medical laboratory science an avenue to build a professional career. We wish all students and educators who use this book the best to carry on a tradition of excellence!

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foreword to the seventh edition

You should not be surprised to learn that the delivery of health care has been undergoing major transformation for several decades. The clinical laboratory has been transformed in innumerable ways as well. At one time, the laboratory students' greatest asset was motor ability. That is not the case any longer. Now the need is for a laboratory professional who is well educated, an analytical thinker, and problem solver, and one who can add value to the information generated in the laboratory regarding a specific patient.

This change impacts the laboratory professional in a very positive manner. Today the students' greatest asset is their mental skill and their ability to acquire and apply knowledge. The laboratory professional is now considered a knowledge worker, and a student's ability to successfully become this knowledge worker depends on their instruction and exposure to quality education. Herein lies the need for the seventh edition of *Clinical Chemistry: Principles, Techniques, and Correlations*. It contributes to the indispensable solid science foundation in medical laboratory sciences and the application of its principles in improving patient outcomes needed by the laboratory professional of today. This edition provides not only a comprehensive understanding of clinical chemistry but also the foundation upon which all the other major laboratory science disciplines can be further understood and integrated. It does so by providing a strong discussion of organ function and a solid emphasis on pathophysiology, clinical correlations, and differential diagnosis. This information offers a springboard to better understand the many concepts related to the effectiveness of a particular test for a particular patient.

Reduction of health care costs, while ensuring quality patient care, remains the goal of health care reform efforts. Laboratory information is a critical element of such care. It is estimated that $65 billion is spent each year to perform more than 4.3 billion laboratory tests. This impressive figure has also focused a bright light on laboratory medicine, and appropriate laboratory test utilization is now under major scrutiny. The main emphasis is on reducing costly overutilization and unnecessary diagnostic testing; however, the issue of under- and misutilization of laboratory tests must be a cause for concern as well. The role of laboratorians in providing guidance to clinicians regarding appropriate test utilization is becoming not only accepted but also welcomed as clinicians try to maneuver their way through an increasingly complex and expensive test menu. These new roles lie in the pre- and postanalytic functions of laboratorians. The authors of this text have successfully described the importance of these phases as well as the more traditional analytic phase. It does not matter how precise or accurate a test is during the analytic phase if the sample has been compromised or if an inappropriate test has been ordered on the patient. In addition, the validation of results with respect to a patient's condition is an important step in the postanalytic phase. Participation with other health care providers in the proper interpretation of test results and appropriate follow-up will be important abilities of future graduates as the profession moves into providing greater consultative services for a patient-centered medical delivery system. Understanding these principles is a necessary requirement of the knowledge worker in the clinical laboratory. This significant professional role provides effective laboratory services that will improve medical decision making and thus patient safety while reducing medical errors. This edition of *Clinical Chemistry: Principles, Techniques, and Correlations* is a crucial element in graduating such professionals.

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Make no mistake: There are few specialties in medicine that have a wider impact on today's health care than laboratory medicine. For example, in the emergency room, a troponin result can not only tell an ER physician if a patient with chest pain has had a heart attack but also assess the likelihood of that patient suffering an acute myocardial infarction in 30 days. In the operating room during a parathyroidectomy, a parathyroid hormone assay can tell a surgeon that it is appropriate to close the procedure because he has successfully removed all of the affected glands or go back and look for more glands to excise. In labor and delivery, testing for pulmonary surfactants from amniotic fluid can tell an obstetrician if a child can be safely delivered or if the infant is likely to develop life-threatening respiratory distress syndrome. In the neonatal intensive care unit, measurement of bilirubin in a premature infant is used to determine when the ultraviolet lights can be turned off. These are just a handful of the thousands of medical decisions that are made each day based on results from clinical laboratory testing.

Despite our current success, there is still much more to learn and do. For example, there are no good laboratory tests for the diagnosis of stroke or traumatic brain injury. The work on Alzheimer's and Parkinson's disease prediction and treatment is in the early stages. And when it comes to cancer, while our laboratory tests are good for monitoring therapy, they fail in the detection of early cancer, essential for improving treatment and prolonging survival. Finally, personalized medicine including pharmacogenomics will play an increasingly important role in the future. Pharmacogenomic testing will be used to select the right drug at the best dose for a particular patient in order to maximize efficacy and minimize side effects.

If you are reading this book, you are probably studying to be a part of the field. As a clinical chemist for over 30 years, I welcome you to our profession.

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Preface

Clinical chemistry continues to be one of the most rapidly advancing areas of laboratory medicine. Since the initial idea for this textbook was discussed in a meeting of the Biochemistry/Urinalysis section of ASMT (now ASCLS) in the late 1970s, the only constant has been changed. New technologies and analytical techniques have been introduced, with a dramatic impact on the practice of clinical chemistry and laboratory medicine. In addition, the health care system is rapidly changing. There is ever increasing emphasis on improving the quality of patient care, individual patient outcomes, financial responsibility, and total quality management. Now, more than ever, clinical laboratorians need to be concerned with disease correlations, interpretations, problem solving, quality assurance, and cost-effectiveness; they need to know not only the *how* of tests but more importantly the *what, why, and when.* The editors of *Clinical Chemistry: Principles, Techniques, and Correlations* have designed the eighth edition to be an even more valuable resource to both students and practitioners.

Now almost 40 years since the initiation of this effort, the editors have had the privilege of completing the eighth edition with another diverse team of dedicated clinical laboratory professionals. In this era of focusing on metrics, the editors would like to share the following information. The 330 contributors in the 8 editions represent 70 clinical laboratory science programs, 83 clinical laboratories, 13 medical device companies, 4 government agencies, and 3 professional societies. One hundred and thirty contributors were clinical laboratory scientists with advanced degrees. With today's global focus, the previous editions of the text have been translated into at least six languages. By definition, a profession is a calling requiring specialized knowledge and intensive academic preparation to define its scope of work and produce its own literature. The profession of Clinical Laboratory Science has evolved significantly over the past four decades.

The eighth edition of *Clinical Chemistry: Principles, Techniques, and Correlations* is comprehensive, up-to-date, and easy to understand for students at all levels. It is also intended to be a practically organized resource for both instructors and practitioners. The editors have tried to maintain the book's readability and further improve its content. Because clinical laboratorians use their interpretative and analytic skills in the daily practice of clinical chemistry, an effort has been made to maintain an appropriate balance between analytic principles, techniques, and the correlation of results with disease states.

In this edition, the editors have maintained features in response to requests from our readers, students, instructors, and practitioners. Ancillary materials have been updated and expanded. Chapters now include current, more frequently encountered case studies and practice questions or exercises. To provide a thorough, up-to-date study of clinical chemistry, all chapters have been updated and reviewed by professionals who practice clinical chemistry and laboratory medicine on a daily basis. The basic principles of the analytic procedures discussed in the chapters reflect the most recent or commonly performed techniques in the clinical chemistry laboratory. Detailed procedures have been omitted because of the variety of equipment and commercial kits used in today's clinical laboratories. Instrument manuals and kit package inserts are the most reliable reference for detailed instructions on current analytic procedures. All chapter material has been updated, improved, and rearranged for better continuity and readability. thePoint*, a Web site with additional case studies, review questions, teaching resources, teaching tips, additional references, and teaching aids for instructors and students, is available from the publisher to assist in the use of this textbook.

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Acknowledgments

A project as large as this requires the assistance and support of many clinical laboratorians. The editors wish to express their appreciation to the contributors of all the editions of *Clinical Chemistry: Principles, Techniques, and Correlations*—the dedicated laboratory professionals and educators whom the editors have had the privilege of knowing and exchanging ideas with over the years. These individuals were selected because of their expertise in particular areas and their commitment to the education of clinical laboratorians. Many have spent their professional careers in the clinical laboratory, at the bench, teaching students, or consulting with clinicians. In these frontline positions, they have developed a perspective of what is important for the next generation of clinical laboratorians.

We extend appreciation to our students, colleagues, teachers, and mentors in the profession who have helped shape our ideas about clinical chemistry practice and education. Also, we want to thank the many companies and professional organizations that provided product information and photographs or granted permission to reproduce diagrams and tables from their publications. Many Clinical and Laboratory Standards Institute (CLSI) documents have also been important sources of information. These documents are directly referenced in the appropriate chapters.

The editors would like to acknowledge the contribution and effort of all individuals to previous editions. Their efforts provided the framework for many of the current chapters. Finally, we gratefully acknowledge the cooperation and assistance of the staff at Wolters Kluwer for their advice and support.

The editors are continually striving to improve future editions of this book. We again request and welcome our readers' comments, criticisms, and ideas for improvement.

Contents

Tracey G. Polsky and Michael J. Bennett

PART one

Basic Principles and Practice of

Clinical Chemistry

1

Basic Principles and Practices

KATHRYN DUGAN and ELIZABETH

WARNING

Chapter Outline

Chapter Objectives

Upon completion of this chapter, the clinical laboratorian should be able to do the following:

Convert results from one unit format to another using the SI and traditional systems. Describe the classifications used for reagent grade water.
Identify the varying chemical grades used in reagent preparation and indicate their correct use. Define primary standard and standard reference materials.
Describe the following terms that are associated with solutions and, when appropriate, provide the respective units: percent, molarity, normality, molality, saturation, colligative properties, redox potential, and conductivity.
Define a buffer and give the formula for pH and p*K* calculations.
Use the Henderson-Hasselbalch equation to determine the missing variable when given either the p*K* and pH or the p*K* and concentration of the weak acid and its conjugate base. List and describe the types of thermometers used in the clinical laboratory.
Classify the type of pipette when given an actual pipette or its description.
Demonstrate the proper use of a measuring and volumetric pipette.
Describe two ways to calibrate a pipetting device.
Define a desiccant and discuss how it is used in the clinical laboratory.
Describe how to properly care for and balance a centrifuge.

Correctly perform the laboratory mathematical calculations provided in this chapter. Identify and describe the types of samples used in clinical chemistry.
Outline the general steps for processing blood samples.
Apply Beer's law to determine the concentration of a sample when the absorbance or change in absorbance is provided.
Identify the preanalytic variables that can adversely affect laboratory results as presented in this chapter.

Key Terms

Analyte
Anhydrous
Arterial blood
Beer's law
Buffer
Centrifugation
Cerebrospinal fluid (CSF)
Colligative property
Conductivity
Deionized water
Deliquescent substance
Delta absorbance
Density
Desiccant
Desiccator
Dilution
Dilution factor
Distilled water
Equivalent weight
Erlenmeyer flasks
Filtration
Graduated cylinder
Griffin Beaker
Hemolysis
Henderson-Hasselbalch
equation Hydrate
Hygroscopic
Icterus
International unit
Ionic strength
Lipemia
Molality
Molarity

Normality
One-point calibration
Osmotic pressure
Oxidized
Oxidizing agent
Percent solution
pH
Pipette
Primary standard
Ratio
Reagent grade water
Redox potential
Reduced
Reducing agent
Reverse osmosis
Serial dilution
Serum
Significant figures
Solute
Solution
Solvent
Specific gravity
Standard
Standard reference materials
(SRMs) Système International
d'Unités (SI) Thermistor
Ultrafiltration
Valence
Whole blood

The primary purpose of a clinical chemistry laboratory is to perform analytic procedures that yield accurate and precise information, aiding in patient diagnosis and treatment. The achievement of reliable results requires that the clinical laboratory scientist be able to correctly use basic supplies and equipment and possess an understanding of fundamental concepts critical to any analytic procedure. The topics in this chapter include units of measure, basic laboratory supplies, and introductory laboratory mathematics, plus a brief discussion of specimen collection, processing, and reporting.

UNITS OF MEASURE

Any meaningful *quantitative* laboratory result consists of two components: the first component represents the number related to the actual test value and the second is a label identifying the units. The unit defines the physical quantity or dimension, such as mass, length, time, or volume.[1] Not all laboratory tests have well-defined units, but whenever possible, the units used should be reported.

Although several systems of units have traditionally been utilized by various scientific divisions, the **Système International d'Unités (SI)**, adopted internationally in 1960, is preferred in scientific literature and clinical laboratories and is the only system employed in many countries. This system was devised to provide the global scientific community with a uniform method of describing physical quantities. The SI system units (referred to as *SI units*) are based on the metric system. Several subclassifications exist within the SI system, one of which is the *basic unit*. There are seven basic units (Table 1.1), with length (meter), mass (kilogram), and quantity of a substance (mole) being the units most frequently encountered. Another set of SI-recognized units is termed *derived units*. A derived unit, as the name implies, is a derivative or a mathematical function describing one of the basic units. An example of an SI derived unit is meters per second (m/s), used to express velocity. Some non-SI units are so widely used that they have become acceptable for use within the SI system (Table 1.1). These include long-standing units such as hour, minute, day, gram, liter, and plane angles expressed as degrees. The SI uses **standard** *prefixes* that, when added to a given basic unit, can indicate decimal fractions or multiples of that unit (Table 1.2). For example, 0.001 liter can be expressed using the prefix *milli*, or 10^{-3}, and since it requires moving the decimal point three places to the right, it can then be written as 1 milliliter, or abbreviated as 1 mL. It may also be written in scientific notation as 1×10^{-3} L. Likewise, 1,000 liters would use the prefix of kilo (10^3) and could be written as 1 kiloliter or expressed in scientific notation as 1×10^3 L.

TABLE 1.1 SI Units

Base Quantity	Name	Symbol
Length	Meter	m
Mass	Kilogram	kg
Time	Second	s
Electric current	Ampere	A
Thermodynamic temperature	Kelvin	K
Amount of substance	Mole	mol
Luminous intensity	Candela	cd
Selected Derived		
Frequency	Hertz	Hz
Force	Newton	N
Celsius temperature	Degree Celsius	°C
Catalytic activity	Katal	kat
Selected Accepted Non-Si		
Minute (time)	(60 s)	min
Hour	(3,600 s)	h
Day	(86,400 s)	d
Liter (volume)	(1 $dm^3 = 10^{-3}$ m^3)	L
Angstrom	(0.1 nm = 10^{-10} m)	Å

TABLE 1.2 Prefixes Used with SI Units

Factor	Prefix	Symbol	Select Decimals
10^{-18}	atto	a	—
10^{-15}	femto	f	—
10^{-12}	pico	p	—
10^{-9}	nano	n	—
10^{-6}	micro	μ	0.000001
10^{-3}	milli	m	0.001
10^{-2}	centi	c	0.01
10^{-1}	deci	d	0.1
10^{0}	Liter, meter, gram	Basic unit	1.0
10^{1}	deka	da	10.0
10^{2}	hecto	h	100.0
10^{3}	kilo	k	1,000.0
10^{4}	mega	M	—
10^{9}	giga	G	—
10^{12}	tera	T	—
10^{15}	peta	P	—
10^{18}	exa	E	—

Prefixes are used to indicate a subunit or multiple of a basic SI unit.

It is important to understand the relationship these prefixes have to the basic unit. The highlighted upper portion of Table 1.2 indicates prefixes that are smaller than the basic unit and are frequently used in clinical laboratories. When converting between prefixes, simply note the relationship between the two prefixes based on whether you are changing to a smaller or larger prefix. For example, if converting from one liter (1.0 × 10^{0} or 1.0) to milliliters (1.0 × 10^{-3} or 0.001), the starting unit (L) is larger than the desired unit by a factor of 1,000 or 10^{3}. This means that the decimal place would be moved to the *right* three places, so 1.0 liter (L) equals 1,000 milliliters (mL). When changing 1,000 milliliters (mL) to 1.0 liter (L), the process is reversed and the decimal point would be moved three places to the left to become 1.0 L. Note that the SI term for mass is *kilogram*; it is the only basic unit that contains a prefix as part of its name. Generally, the standard prefixes for mass use the term *gram* rather than *kilogram*.

Example 1: Convert 1.0 L to μL

1.0 L (1×10^0) = ? μL (micro = 10^{-6}); move the decimal place six places to the right and it becomes 1,000,000 μL; reverse the process to determine the expression in L (move the decimal six places to the left of 1,000,000 μL to get 1.0 L).

SI CONVERSIONS

To convert between SI units, move the decimal by the difference between the exponents represented by the prefix either to the right (from a larger to a smaller unit) or to the left (from a smaller to a larger one) of the number given:

decimal point

←000 #.000→

smaller to larger unit larger to smaller unit

Convert to larger unit: smaller to larger unit—move to the left

Convert to a smaller unit: larger to smaller—move to the right

= the numeric value given

Example 2: Convert 5 mL to μL

5 mL (milli = 10^{-3}, larger) = ? μL (micro = 10^{-6}, smaller); move the decimal by three places to the right and it becomes 5,000 μL.

Example 3: Convert 5.3 mL to dL

5.3 mL (milli = 10^{-3}, smaller) = ? dL (deci = 10^{-1}, larger); move the decimal place by two places to the left and it becomes 0.053 dL.

Reporting of laboratory results is often expressed in terms of substance concentration (e.g., moles) or the mass of a substance (e.g., mg/dL, g/dL, g/L, mmol/L, and IU) rather than in SI units. These familiar and traditional units can cause confusion during interpretation. Appendix D (on thePoint), *Conversion of Traditional Units to SI Units for Common Clinical Chemistry Analytes*, lists both reference and SI units together with the conversion factor from traditional to SI units for common analytes. As with other areas of industry, the laboratory and the rest of medicine are moving toward adopting universal standards promoted by the International Organization for Standardization, often referred to as ISO. This group develops standards of practice, definitions, and guidelines that can be adopted by everyone in a given field, providing for more uniform terminology and less confusion. Many national initiatives have recommended common units for laboratory test results, but none have been widely adopted.[2] As with any transition, clinical laboratory scientists should be familiar with all the terms currently used in their field.

REAGENTS

In today's highly automated laboratory, there seems to be little need for reagent preparation by the clinical laboratory scientist. Most instrument manufacturers make the reagents in a ready-to-use form or “kit” where all necessary reagents and respective storage containers are prepackaged as a unit requiring only the addition of water or buffer to the prepackaged components for reconstitution. A heightened awareness of the hazards of certain chemicals and the numerous regulatory agency requirements has caused clinical chemistry laboratories to readily eliminate massive stocks of chemicals and opt instead for the ease of using prepared reagents. Periodically, especially in hospital laboratories involved in research and development, biotechnology applications, specialized analyses, or method validation, the laboratorian may still face preparing various reagents or solutions.

Chemicals

Analytic chemicals exist in varying grades of purity: analytic reagent (AR); ultrapure, chemically pure (CP); United States Pharmacopeia (USP); National Formulary (NF); and technical or commercial grade.[3] A committee of the American Chemical Society (ACS) established specifications for AR grade chemicals, and chemical manufacturers will either meet or exceed these requirements. Labels on reagents state the actual impurities for each chemical lot or list the maximum allowable impurities. The labels should be clearly printed with the percentage of impurities present and either the initials *AR* or *ACS* or the term *For laboratory use* or *ACS Standard-Grade Reference Materials*. Chemicals of this category are suitable for use in most analytic laboratory procedures. Ultrapure chemicals have been put through additional purification steps for use in specific procedures such as chromatography, atomic absorption, immunoassays, molecular diagnostics, standardization, or other techniques that require extremely pure chemicals. These reagents may carry designations of HPLC (high-performance liquid chromatography) or chromatographic on their labels.

Because USP and NF grade chemicals are used to manufacture drugs, the limitations established for this group of chemicals are based only on the criterion of not being injurious to individuals. Chemicals in this group may be pure enough for use in most chemical procedures; however, it should be recognized that the purity standards are not based on the needs of the laboratory and, therefore, may or may not meet all assay requirements.

Reagent designations of CP or pure grade indicate that the impurity limitations are not stated and that preparation of these chemicals is not uniform. It is not recommended that clinical laboratories use these chemicals for reagent preparation unless further purification or a reagent blank is included. Technical or commercial grade reagents are used primarily in manufacturing and should never be used in the clinical laboratory.

Organic reagents also have varying grades of purity that differ from those used to classify inorganic reagents. These grades include a practical grade with some impurities; CP, which approaches the purity level of reagent grade chemicals; spectroscopic (spectrally pure) and chromatographic grade organic reagents, with purity levels attained by their respective procedures; and reagent grade (ACS), which is certified to contain impurities below certain levels established by the ACS. As in any analytic method, the desired organic reagent purity is dictated by the particular application.

Other than the purity aspects of the chemicals, laws related to the Occupational Safety and Health Administration (OSHA)[4]require manufacturers to indicate any physical or biologic health hazards and precautions needed for the safe use, storage, and disposal of any chemical. A manufacturer is required to provide technical data sheets for each chemical manufactured on a document