CLINICAL DISORDERS OF FLUID AND ELECTROLYTE METABOLISM

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FOREWORD

This volume is one of a series being published by the Blakiston Division of McGraw-Hill, based on postgraduate symposia and courses offered by the Division of Continuing Education in Medicine and Health Sciences at the University of California (Los Angeles) School of Medicine.

Since it is the policy of this department to offer seminars and symposia on current topics in which there is new diagnostic or therapeutic material available, it seemed highly desirable to have the proceedings edited and published. The merit in this approach to medical publication has been amply demonstrated by the reception of previous volumes: "The Differential Diagnosis of Abdominal Pain," edited by Sherman M. Mellinkoff, M.D.; "Modern Dermatologic Therapy," edited by Victor D. Newcomer, M.D., and myself; "Treatment of Emotional Problems in Office Practice," edited by Frank Tallman, M.D.; "Sterility: Office Management of the Infertile Couple," edited by Edward T. Tyler, M.D.; "Management of Medical Emergencies," edited by John C. Sharpe, M.D.; and "Clinical Uses of Adrenal Steroids," edited by Josiah Brown, M.D., and Carl M. Pearson, M.D.

We feel that these volumes in the UCLA Medical Extension Series, of which this is the seventh, will be of practical value to the physician who wishes to have at hand a general coverage of the subject with which he is concerned.

Thomas H. Sternberg, M.D.,
Assistant Dean in Charge of Postgraduate Medical Education; Chairman, Editorial Committee, UCLA Medical Extension Series

SECOND FOREWORD

In the last few years no area in internal medicine has attracted as much interest or provided more practical returns than research on water and electrolyte composition of the several compartments of the body in normal and in disease states. Innumerable papers and not a few monographs have been published on the subject, and now most of the data fit together to afford a basis for physiologic integration.

This book, edited by Morton H. Maxwell and Charles R. Kleeman (who also contributed four chapters to it), is informed without being complex: it aims at clarity, simplicity, and a full statement of fundamental facts and principles without at any time giving the appearance of unwarranted erudition. It is unusually comprehensive. All the authors are experienced in their respective fields, possess good insight into clinical situations, and write in a style suited to the reader who wants the over-all picture rather than the experimental details. Each author has been cautious at the difficult crossroads, but without leaving everything up in the air. Though avoiding the difficult, if not impossible, task of completely documenting references to all the pertinent original papers, the selected bibliography is an adequate guide to the recent source material for anyone with specialized interests.

Doctors Maxwell and Kleeman and their collaborators are to be congratulated on producing what I am tempted to call an elementary treatise in what is certainly not an elementary field: the diverse physiologic and pathophysiologic topics discussed in "Clinical Disorders of Fluid and Electrolyte Metabolism" could not conceivably be presented competently by any one man. As a collection of essays the volume is unique in that it maintains almost complete uniformity of style with a minimum of repetition.

I am happy, therefore, to add this short foreword to this monumental work.

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PREFACE

The rapid accumulation of information on fluid and electrolyte metabolism in recent years has demonstrated the importance of this subject in in every branch of medicine. Acute renal failure, edema, or potassium depletion, for example, may occur in infants, in pregnant women, in postsurgical patients, or in chronically debilitated individuals. A practical working knowledge of this field has therefore become essential for every practicing physician.

Consequently, several years ago a comprehensive postgraduate course in fluid and electrolytes was started at the University of California in Los Angeles. The enthusiasm of the response emphasized the desire among physicians of every medical specialty for a better understanding of this subject. As an outgrowth of this successful course, "Clinical Disorders of Fluid and Electrolyte Metabolism," the first multiauthored text in this field, was written. This approach has made it possible for each of the major aspects to be discussed authoritatively by individuals carefully selected because of their teaching and research activities.

Obviously, complete uniformity of style and concept cannot be achieved with multiple contributors. However, to our knowledge there are no major contradictions, and the overlapping and repetition which occur were intentionally permitted, to emphasize certain important principles or clinical entities. Each of the clinical chapters contains a brief discussion of the basic physiologic concepts necessary for its understanding and may therefore be profitably read individually. It is suggested, however, that the reader will derive maximum benefit from the book by first studying the initial six chapters. Although the entire field of fluid and electrolyte metabolism, including all of the major recent contributions, is covered extensively, in general only key references have been included. A chapter dealing specifically with surgery was omitted because of several recent extensive monographs on this subject. It should be emphasized, however, that the principles presented in this book are applicable to the surgical as well as to the medical patient.

It has been our aim to compile a text which will be of value not only to the practicing physician but also to the medical student in his preclinical and clinical years.

The editors thank Dorothy Wilson for invaluable secretarial assistance and Dr. Arthur Gordon for assuming the laborious and difficult task of assisting with the editing, proofreading, and indexing.

Morton H. Maxwell
Charles R. Kleeman

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Morton H. Maxwell
Charles R. Kleeman

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DYNAMICS OF BODY WATER AND ELECTROLYTES

A *solution* can be defined as a one-phase system composed of two or more molecular species. In a true solution there are no boundary surfaces between particles of the components of more than molecular size; i.e., no boundary surfaces can be detected, and the phases do not spontaneously separate. The terms *solvent* and *solute* are purely arbitrary, the solvent being that component which is present in the larger proportion. Forty-five to sixty-eight per cent of the human body consists of a dilute aqueous solution in which water is the solvent. The solutes consist of organic and inorganic substances. The concentrations, volumes, distribution, movement, and interrelationships of water and of organic and inorganic electrolytes comprise the subject of this book.

UNITS OF SOLUTE MEASUREMENT

The dynamic equilibria and reactions between the various substances in the body fluids require that these solutes be equated in terms of comparable units of measurement. Different units serve different purposes. In the case of sodium, for example, we may be interested in knowing that the total body sodium of a 70-kg man is about 3,000 *milliequivalents* (mEq), or 69 *grams* (gm), or 40 *milliequivalents per kilogram* (mEq/kg) of body weight. The usual plasma sodium concentration is 140 *milliequivalents per liter* (mEq/L), an important figure for acid-base equilibria. In discussing the integrity of the extracellular fluid volume, however, we must know that sodium contributes 140 *milliosmoles per liter* (mOsm/L).

Any discussion of fluid and electrolytes must be predicated on a complete understanding of the units of measurement.

Atomic Weight

Atomic weight is an arbitrary number. The weight of 1 atom of oxygen was chosen as 16 to be the relative standard of reference. Relative to this standard, sodium has an atomic weight of 23, and chlorine has an atomic weight of 35.5. The proportion by weight[1] of the various elements in a compound can be calculated with the use of atomic weights. For example, in 58.5 gm sodium chloride (NaCl), there are 23 gm sodium and 35.5 gm chlorine. Table 1-1 lists the atomic weights of those elements which occur in the body fluids or are frequently used in biochemical reagents.

Table 1-1. ATOMIC WEIGHTS OF BIOLOGICALLY IMPORTANT ELEMENTS

Element	Symbol	Atomic-weight	Element	Symbol	Atomic weight
Aluminum	Al	26.98	Manganese	Mn	54.94
Bromine	Br	79.92	Mercury	Hg	200.61
Calcium	Ca	40.08	Nitrogen	N	14.01
Carbon	C	12.01	Oxygen	O	16.00
Chlorine	Cl	35.46	Phosphorus	P	30.98
Chromium	Cr	52.01	Potassium	K	39.10
Copper	Cu	63.54	Silver	Ag	107.88
Hydrogen	H	1.01	Sodium	Na	22.99
Iodine	I	126.91	Sulfur	S	32.07
Iron	Fe	55.85	Tungsten	W	183.86
Magnesium	Mg	24.32	Zinc	Zn	65.38

Molecular Weight, Mole, and Millimole

The molecular weight of a substance is the sum of the atomic weights of all the elements specified in the formula of that substance. A *mole* (M) of a substance is its molecular weight expressed in grams, and a *millimole* (mM) is 1/1,000 of a mole, or its weight in milligrams. Because of the small concentrations of most substances in the body fluids, the term millimole is the one most frequently employed. The terms mole and millimole may be used for all substances, regardless of whether they are organic or inorganic, ionized or nonionized. A mole, when applied to an element, is equal to the gram atomic weight of that element. Examples are shown in Table 1-2. Although the concentrations of most of the electrolytes in the body fluids are properly expressed as milliequivalents per liter, in theory calcium and phosphorus should be recorded as millimoles per liter.

The concentrations of gases are also expressed in terms of molecular

[1] Although the term *mass* is technically correct, by convention the word *weight* will be used in its place in this text. Atomic weights will also be rounded off to the nearest 0.5.

Table 1-2. IONIZED AND NONIONIZED SUBSTANCES EXPRESSED AS MOLES AND MILLIMOLES

Substance	Formula	Molecular weight	Mole (M)	Millimole (mM)
Glucose	$C_6H_{12}O_6$	6(12) + 12(1) + 6(16) = 180	180 gm	180 mg
Potassium chloride	KCl	39 + 35.5 = 74.5	74.5 gm	74.5 mg
Sodium bicarbonate	$NaHCO_3$	23 + 1 + 12 + 3(16) = 84	84 gm	84 mg
Calcium chloride	$CaCl_2$	40 + 2(35.5) = 111	111 gm	111 mg
Ammonium chloride	NH_4Cl	14 + 4(1) + 35.5 = 53.5	53.5 gm	53.5 mg
Bicarbonate	HCO_3^-	1 + 12 + 3(16) = 61	61 gm	61 mg
Sulfate	SO_4^-	32 + 4(16) = 96	96 gm	96 mg
Sodium ion	Na^+		23 gm	23 mg
Calcium ion	Ca^{++}		40 gm	40 mg

equivalents. One mole of any gas (e.g., oxygen, carbon dioxide, nitrous oxide, etc.) under standard conditions of temperature and pressure occupies a constant volume of 22.4 L, or 1 mM occupies 22.4 ml. Carbon dioxide (CO_2), the gas which is most important in electrolyte balance, is expressed as millimoles per liter. This is often used interchangeably with milliequivalents per liter, because presumably 1 mM CO_2 will form 1 mEq HCO_3^-.

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^- \qquad (1\text{-}1)$$

This assumption is not completely true, however, since in some situations bicarbonate conceivably could partially dissociate to hydrogen and a carbonate ion. However, this reaction is minimal below a pH of 8 and therefore is of little physiologic consequence.

$$H^+ + HCO_3^- \rightleftharpoons H^+ + H^+ + CO_3^- \qquad (1\text{-}2)$$

Carbon dioxide content (or combining power) is therefore preferably expressed as millimoles per liter. Carbon dioxide is still occasionally expressed as volumes per cent (vol per cent),[2] i.e., milliliters of CO_2 gas/100 ml of blood. To convert volumes per cent of carbon dioxide to millimoles per liter, the following formula may be used:

$$\text{mM } CO_2/L = \frac{\text{vol per cent } CO_2 \times 10}{22.4} \qquad (1\text{-}3)$$

[2] *Per cent* means "per hundred." Therefore, any concentration expressed as per cent refers to units/100 ml solution. By usage, most of the therapeutic solutions of electrolytes are expressed gravimetrically per 100 ml water. Thus "0.9 per cent saline" refers to 0.9 gm sodium chloride/100 ml water, and "5 per cent glucose solution" means 5 gm dextrose/100 ml water, i.e., 50 gm/L. To make it more confusing, however, some solutions are also equated in terms of "normal," or "isotonic," and still others in terms of moles per liter, i.e., "a ⅙ molar lactate solution" contains ⅙ of a mole of sodium lactate per liter of water. Also by convention, most of the nonelectrolytes of the body fluids (e.g., glucose, urea, creatinine, uric acid, cholesterol) are expressed as milligrams per cent, or mg/100 ml, of blood or plasma. A blood glucose concentration of 80 mg per cent means 80 mg glucose/100 ml blood.

Electrochemical Equivalence—Milliequivalents

Electrolytes combine with each other in proportion to their ionic valence, rather than in proportion to their weights. Chemically, the standard of reference is the electrical charge (+) of 1 atomic weight (1 gm) of hydrogen. *One equivalent (Eq) of an ion is that amount which can replace or combine with one gram of hydrogen;* this amount of the ion is therefore chemically "equivalent" to one gram of hydrogen. Expressed differently, *1 Eq of a substance is the atomic, or formula, weight divided by the ionic valence* and provides a quantitative index of the combining proportions of all ionic species. The electrolyte concentrations in the dilute body fluids are more easily expressed as *milliequivalents (1 mEq equals 1/1,000 Eq).*

The principle of electrochemical equivalence may be illustrated as follows: 1 mM sodium is 23 mg, and 1 mM chlorine is 35.5 mg. If we were to add 23 mg sodium and 35.5 mg chlorine to 1 L water, we would have a millimolar solution of sodium chloride:

$$\underset{(1\ mM)}{23\ mg\ Na^+} + \underset{(1\ mM)}{35.5\ mg\ Cl^-} \longrightarrow \underset{(1\ mM)}{58.5\ mg\ NaCl} \qquad (1\text{-}4)$$

If we were to add *equal weights* of sodium and chlorine, however, there would be an excess of sodium ion in solution:

$$35.5\ mg\ Na^+ + 35.5\ mg\ Cl^- \longrightarrow 58.5\ mg\ NaCl + 12.5\ mg\ Na^+ \qquad (1\text{-}5)$$

Electrolytes do not combine gram for gram or milligram for milligram; they combine equivalent for equivalent, or milliequivalent for milliequivalent. In the case of univalent ions, 1 Eq equals 1 M, and 1 mEq equals 1 mM. In Equation 1-4, therefore, 1 mEq sodium reacted with 1 mEq chlorine.

Multivalent ions have a greater chemical combining power than univalent ions. Since electrochemical neutrality must be preserved in all reactions, a divalent ion, which has two electrical charges, will react with two univalent ions. Therefore 1 mM of a divalent ion supplies 2 mEq; i.e., 1 mM calcium (2 mEq) reacts with 2 mM chloride (2 mEq) in the reaction

$$Ca^{++} + 2\ Cl^- \rightleftharpoons CaCl_2 \qquad (1\text{-}6)$$

It is apparent that 1 mM of a substance will contain 3 mEq if the valence is 3.

Dividing the number of milligrams of a univalent electrolyte by its molecular (or atomic) weight yields the number of milliequivalents. For example, 23 mg sodium divided by the atomic weight of sodium (23) yields a value of 1; i.e., 23 mg sodium contain 1 mEq. With multivalent substances, the numerator must be multiplied by the valence; i.e., 40 mg calcium multiplied by its valence ($40 \times 2 = 80$) and divided by its atomic weight ($80 \div 40$) yields 2 mEq. Since in the interpretation of laboratory

results we are largely concerned with converting milligrams per cent, or milligrams *per 100 ml*, to milliequivalents *per liter*, the numerator must be multiplied by 10. The final equation then becomes

$$\frac{\text{mg per cent}}{\text{atomic weight}} \times \text{valence} \times 10 = \text{mEq/L} \qquad (1\text{-}7)$$

The utility of expressing most of the electrolyte concentrations in milliequivalents per liter is apparent from Table 1-3.

Table 1-3. NORMAL PLASMA ELECTROLYTE CONCENTRATIONS

Electrolyte	Milligrams per 100 milliliters	Milliequivalents per liter
Cations:		
Sodium	326	142
Potassium	16	4
Calcium	10	5
Magnesium	2.5	2
Total cations	354.5	153
Anions:		
Chloride	362	101
Bicarbonate	60	27
Phosphate	3.5	2
Sulfate	1.5	1
Organic acids	15	6
Protein	7,000	16
Total anions	7,442	153

The total concentration of cations is equal to that of the anions, and electroneutrality exists. When expressed as milligrams per cent, however, gross inequality exists, and nothing useful is learned about chemical interrelationships. The largest component, by weight, in the anion column is protein, which in terms of acid-base balance is seldom of importance.

Having emphasized the greater utility of electrochemical as opposed to gravimetric concentrations, it must be pointed out that even the term *milliequivalents per liter* is not ideally applicable for all the electrolytes in all circumstances. In problems of calcium and phosphorous metabolism, for example, these ions are properly measured as millimoles per liter. The ionized (diffusible) calcium fraction depends on the proportion of calcium not bound to plasma proteins; the usual laboratory determination includes all the serum calcium and is not properly expressed as milliequivalents per liter.[3] Serum "phosphorus" consists of variable proportions

[3] Serum calcium *can* be accurately recorded as milliequivalents per liter if the total number of milliequivalents is partitioned into ionized and nonionized fractions; the nonionized fraction may then be classified into calcium proteinates and other nonionized components of calcium salts, such as citrates and phosphates.

of phosphate, mono- and dihydrogen phosphate ($PO_4^{=}$, HPO_4^{-}, $H_2PO_4^{-}$), so that no valence can be assigned to this substance. Plasma proteins are usually expressed as *grams per cent* (gm per cent), or gm/100 ml plasma (see footnote 2). Although they are included in the anion column (Table 1-3), their electrochemical equivalence is affected by pH and other factors; they may even act at times as weak cations.

Osmoles and Milliosmoles

The concepts of osmosis, osmotic pressure, effective osmotic pressure, and oncotic pressure will be described in a succeeding section. The osmotic effect of a substance in solution depends only on the number of particles dissolved and is independent of their weight, electrical charge, valence, or chemical formula. This is based upon the fact that 1 M of any element, regardless of weight, contains the same number of molecules (Avogadro's number: 6.061×10^{23} particles/M). If a molecule in solution dissociates into 2 or 3 particles, the osmotic pressure is doubled or tripled, respectively. Units of osmotic force are conveniently expressed as *osmoles* (Osm) and *milliosmoles* (mOsm).

For substances which do not dissociate into smaller parts (e.g., glucose, urea), 1 M equals 1 Osm, and 1mM equals 1 mOsm. This also applies to substances which carry electrical charges; i.e., 1 mM of sodium (23 mg) equals 1 mOsm. It is obvious in the case of sodium that 1 mOsm also equals 1 mEq. Divalent and trivalent ions exert no more osmotic pressure than univalent ions, despite their differing chemical equivalences. Thus, for magnesium (Mg^{++}): 1mM (24.5 mg) = 1mOsm = 2 mEq; for phosphate ($PO_4^{=}$): 1mM (95 mg) = 1 mOsm = 3 mEq. One millimole of sodium chloride (58.5 mg), which dissociates into sodium and chloride in solution, contributes twice as many osmotically active particles as a non-ionized substance, so that 1 mM = 2 mEq = 2 mOsm.

Summary

The essential points to remember about the units of measurement are:

1. A *millimole* equals 1/1,000 of the gram atomic, or molecular, weight of a substance and is independent of valence.
2. A *milliequivalent* equals 1/1,000 of an equivalent, which is the gram formula weight divided by the ionic valence, or the electrochemical combining power of 1 gm atom of hydrogen. If the valence is 2 or 3, 1 mM contains 2 or 3 mEq.
3. A *milliosmole* equals 1/1,000 of an osmol. It is independent of valence, electrical charge, or mass, and is a measure of the number of discrete particles in solution.

These relationships may be clarified by referring to Table 1-4.