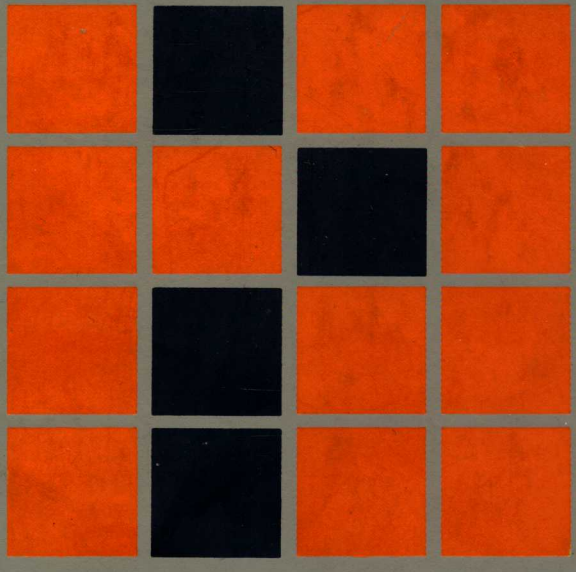
Water, Electrolyte and Acid–Base Metabolism

DIAGNOSIS AND MANAGEMENT

SECOND EDITION



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J. B. Lippincott Company

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The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

To Peggy Carroll and Chung Oh
and to
Angela (and Danny, Sean, and Kathleen), Gina (and Michael), Hughie, Frank, Mimi (and Sarah), Paul and Maria; and John and Anne

Preface

The success enjoyed by the first edition of *Water, Electrolyte and Acid–Base Metabolism* has persuaded us that our approach to teaching with this form of communication is valid: to lay the groundwork for understanding of clinical disease with discussions of pathophysiology that are within the grasp of serious students of medicine but do not offend their intelligence with oversimplification. As we continue to bring this message to the classroom, the ward, and the community hospital, it has become clear to us that, in addition to bringing the material up to date, we ought to make a special effort to deal with certain areas of pathophysiology that even good students and interested physicians fairly consistently fail to grasp. Therefore, we have rewritten virtually the entire text, with special attention given to those problem areas identified through repeated encounters with students, residents, nephrology fellows, and practicing physicians.

Advances in the areas of renal physiology and the pathophysiology of water, electrolyte, and acid–base metabolism have been of striking magnitude and, at times, distressing complexity. The material we have recorded here has been well worked over, with an eye to precision, clinical importance, and readiness of understanding. We have received a fair amount of friendly prodding over the last few years to bring forth this edition, and we trust that it will meet the expectations of students at all levels of the medical educational process who have awaited it.

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Preface to the First Edition

This text is the outgrowth of the authors' experience in teaching at a medical center where the training of clinical and research fellows, house staff, and students is of paramount concern but where the needs of the community physicians are also met by a very active program of continuing education. We are persuaded that pathophysiology is not only a fascinating discipline but the heart of diagnostic and therapeutic medicine, and we have attempted to carry this philosophy into the classroom, the ward, and the community hospital. It is our hope that the material we have recorded here will be interesting and useful to those who practice medicine as well as those in training. We have tried to keep the tone amiably scientific without being ponderous, so that the concepts will be within the grasp of all the readers and, most importantly, so that the sections on diagnosis and therapy will flow smoothly and logically from the sections on mechanisms of disease.

The early chapters on basic principles and renal physiology are, we believe, worthy of the reader's time even if the going may be a bit slow here and there; an understanding of body composition and renal physiology provides a secure groundwork for the subsequent chapters on specific areas of physiology and disease.

The lecturer can shift his gears and adjust his pace to suit his audience, but he who would write a textbook aimed at students, house staff, practicing physicians and nephrology fellows must select one pace and one style to suit all, and at times his skill in exposition is sorely tried. To the extent that we succeed we are grateful.

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Contents

Chapter 1

Electrolyte Physiology and Body Composition

PRINCIPLE OF OSMOSIS

The body fluid is an aqueous solution of electrolytes and nonelectrolytes, whose behavior may be readily predicted by understanding the principles of osmosis. The mechanism of osmosis may be explained in the following manner: When particles are dissolved in water, each particle, regardless of its size or charge, must be surrounded by an equal fraction of available water, whether that particle be a sodium ion, a bicarbonate ion, a molecule of glucose, a molecule of urea, a molecule of protein, or another molecule. If two solutions are separated by a membrane that will permit water, but not solute, to pass through its pores (semipermeable membrane), water will move from the more dilute to the more concentrated solution to achieve osmotic equilibrium (Fig. 1-1).

The body fluid is composed of two solutions, one outside of and one inside of the cells. These solutions, the extracellular fluid (ECF) and the intracellular fluid (ICF), are separated by the cell membrane. Part of the solution outside of the cells is held within the blood vessels to serve as a vehicle for erythrocytes and other blood components (plasma water). Most of the remainder of the ECF is the interstitial fluid (ISF), a compartment that subserves the transfer of nutrients and products of metabolism between the plasma and the cells. The functional unit of the body, the cell, consists of a solution of proteins, salts, and small organic molecules, all surrounded by a membrane. Within the cell, the processes of chemical synthesis and degradation that define life take place. If these processes are to proceed in the normal fashion, a chemical milieu is required that is defined by such parameters as pH, oxygen concentration, temperature, and solute concentration; gross deviation is not compatible with life.

The constancy of volume of extracellular fluid and intracellular fluid is achieved

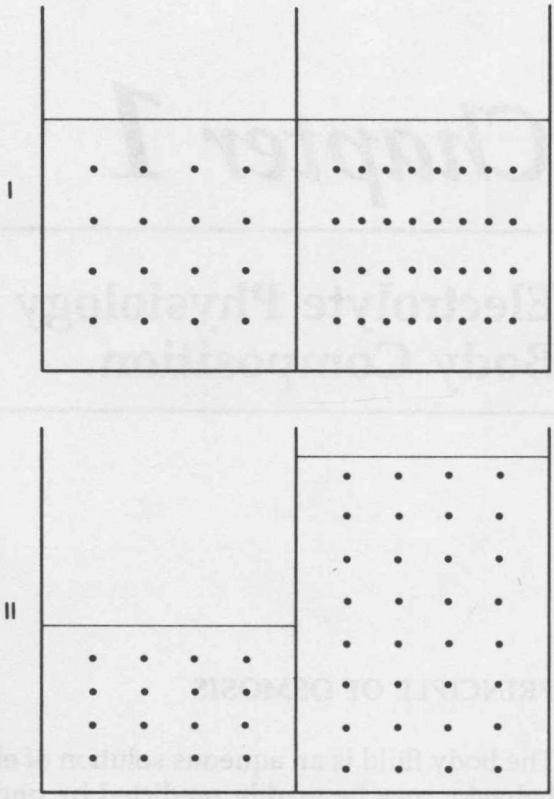

FIGURE 1-1. Achievement of osmotic equilibrium. In panel *I* the quantity of solute added to the compartment on the right is twice that added to the left compartment. In panel *II* water has shifted so that the ratio of solute to water is identical in the two compartments.

by the presence of solutes that are, for all practical purposes, restricted to one or the other compartment. Although the nature of the solutes differs between the two compartments, the total concentration of the solutes is kept the same on both sides of the cell membrane through osmotic equilibrium.

UNITS OF MEASUREMENT

Although an effort is under way to achieve international standardization (molality) for units of concentrations of biologic solutes, most laboratories still report values in time-honored units. The units of concentration most frequently used are milligrams per 100 milliliters (mg/100 mL) or a deciliter (mg/dL or mg%), and milliequivalents per liter (mEq/L). When the term *percent* (%) is used without specifying the weight unit, as in 5% glucose solution and 10% calcium chloride solution, it refers to grams per 100 mL. The terms *equivalent* and *milliequivalent* are used only for electrolytes. One equivalent of any electrolyte carries the same number of electrical charges as 1 gram of hydrogen ion. One gram atomic weight or gram molecular weight of any substance has the same number of atoms or molecules as 1 gram of hydrogen. Therefore,

$$\frac{\text{Atomic weight or molecular weight (in grams)}}{\text{valence}} = 1 \text{ equivalent.}$$

The concentrations of nonelectrolytes, such as glucose and urea are, at present, still expressed in mg/dL or g/dL. Concentrations of monovalent ions such as sodium, potassium, bicarbonate, and chloride are expressed in mEq/L, and multivalent ions such as calcium, magnesium, and phosphate may be expressed in either mg/dL or mEq/L.

One gram molecular weight (mole) has the same number of molecules as 1 mole of any other substances. The number of particles provided by 1 mole of a substance in solution depends on the number of particles produced upon dissociation of the substance. If a substance dissociates into two particles, 1 mole of such substance, for example, NaCl, will produce the same number of particles as 2 moles of a substance that does not dissociate, for example, glucose. The term *osmol* refers to the unit based on the number of particles. Thus, 1 mole of a nondissociating substance, for example, glucose, equals 1 osmol, but 1 mole of NaCl produces 2 osmols, and 1 mole of H_2SO_4 produces 3 osmols. One osmol is 1000 milliosmols (mosm).

The chemical determination of the osmotic concentration of a body fluid (plasma, urine, and the like) is made by measuring the depression of freezing point or elevation of vapor pressure, which are *colligative* properties, that is, properties that depend on particle concentration. The terms *osmolarity* and *osmolality* are used almost interchangeably when referring to the osmotic concentration of a solution. Defined with precision, **osmolarity** refers to the number of milliosmols in 1 L of solution, whereas osmolality refers to the number of milliosmols in 1 kg of water. **Osmolality** is the preferred term because the colligative property depends on the number of particles in a given volume of water. The following relationships will be obvious.

1. $\dfrac{\text{mg/dL} \times 10}{\text{molecular (or atomic) weight}}$ or $\dfrac{\text{mg/dL}}{\text{molecular weight/10}} = \text{mmol/L}$
2. mmol/L × a = mosm/L, where *a* is the number of particles into which the substance dissociates
3. $\dfrac{\text{mEq}}{\text{valence}} = \text{mmol or mosm,}$

   e.g., $\dfrac{\text{mEq/L of } Na^+}{1}$ or $\dfrac{\text{mEq/L of } Ca^{2+}}{2}$ or $\dfrac{\text{mEq of } PO_4^{3-}}{3} = \text{mosm/L}$

Note: The milliequivalents of ions dissolved in solution are directly translatable into milliosmols only in very dilute solutions, in which ions are completely dissociated. As the concentration of solution increases, completeness of dissociation lessens. The number of measurable particles present (measured osmolality) as a fraction of the number predicted on the assumption of complete dissociation (predicted osmolality) is called the ***osmotic coefficient.*** *The measured osmolality of a 150-mmol solution of sodium chloride is 279 mosm/L, whereas the calculated osmolality is 300 mosm/L; the osmotic coefficient is, therefore, 0.93. The osmotic coefficients of electrolytes vary with the concentration: the higher the concentration, the lower the osmotic coefficient.*

PLASMA ONCOTIC PRESSURE: VAN'T HOFF EQUATION AND DONNAN EQUILIBRIUM

The presence of a relatively impermeant solute, protein, is responsible for the **oncotic pressure (colloid osmotic pressure)** of plasma. Because oncotic pressure is created by the presence of impermeant solutes, plasma oncotic pressure, in theory, should be calculable from the molal concentration of plasma proteins. The van't Hoff equation converts osmolality to osmotic pressure:

$$\pi = CRT,$$

where π is osmotic pressure, C osmolal solute concentration, R the gas constant, and T the absolute temperature. By using the appropriate numbers for the gas constant and the absolute temperature, the van't Hoff equation at 37°C (310 K) can be restated as

$$\pi = 19.3 \times C \text{ mmHg},$$

where C is a solute concentration in mosm/L. The plasma oncotic pressure calculated from the molal concentration of plasma proteins using the above equation, however, is much smaller than oncotic pressure measured with an oncometer. At the normal plasma protein concentration of 0.8 mosm/L (7 g/dL), the plasma oncotic pressure calculated using the foregoing equation is 15.4 (19.3×0.8) mmHg, whereas the normal plasma oncotic pressure directly measured is 23 to 25 mmHg. The difference is explained by the **Donnan equilibrium.**

When two solutions are separated by a membrane permeable to water and small ions, and when one of the solutions contains impermeant ions such as proteins, distribution of permeant ions occurs according to prediction by the Donnan equilibrium. Suppose that solutions 1 and 2 are separated by a membrane that is permeable to water, Na^+, and Cl^-, but not to the protein anions, and that protein anions are restricted to solution 1. The sodium ions in solution 1 (Na_1) must be balanced by both Cl^- and protein, whereas Na_2 is balanced only by Cl^-. Hence $Cl_1 < Cl_2$, whereas $Na_1 > Na_2$. The difference in chloride concentration causes diffusion of Cl^- from solution 2 to solution 1, creating a transmembrane electrical potential (Em) that balances out the chemical (chloride concentration) gradient. The same electrical gradient then predicts the sodium concentration gradient. The **Nernst equation** predicts the choride and sodium concentration gradients at equilibrium:

$$Em = 60 \log Cl_2/Cl_1$$
$$Em = 60 \log Na_1/Na_2$$

At equilibrium, solution 1 will be more negative than solution 2. When the two equations are combined, $60 \log Cl_2/Cl_1 = 60 \log Na_1/Na_2$ and, hence, $Cl_2/Cl_1 = Na_1/Na_2$. Therefore,

$$Na_1 \times Cl_1 = Na_2 \times Cl_2 \text{ (Fig. 1-2).}$$

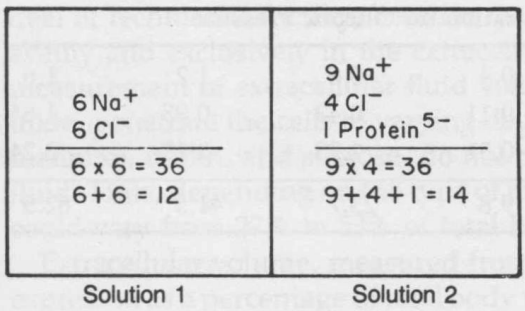

FIGURE 1-2. Donnan equilibrium. The products of diffusible cations and anions are the same in two compartments, but the sums are different.

Because solution 2 contains only Na^+ and Cl^-, $Na_2 = Cl_2$, but because Na^+ in solution 1 is balanced by both Cl^- and protein, $Na_1 > Cl_1$. Thus, mathematically it can be shown that

$$(Na_1 + Cl_1) > (Na_2 + Cl_2).$$

Plasma oncotic pressure is measured by an oncometer by equilibrating plasma against a solution that has the same ionic composition but that does not contain protein. When the plasma containing 156 mEq/L of diffusible cations, 140 mEq/L of diffusible anions, and 16 mEq/L of protein anions is equilibrated against a solution containing no protein, the concentration of diffusible cations and anions of the solution, a, is calculated by the following equation:

$$156 \times 140 = a^2$$
$$a = 147.785.$$

Hence, the sum of the concentrations of diffusible cations and anions in the plasma (156 + 140 = 296) is higher than that of the fluid containing no protein (147.785 + 147.785 = 295.57), and the differnece is 0.43 mmol/L. Thus, the total solute concentration of the plasma is higher than that of the fluid containing no protein, not only because of the protein concentration (0.8 mosm/L), but also because of the higher concentration of diffusible solutes (0.43 mmol/L). The total difference in solute concentration is, therefore, 1.23 mosm/L, and the difference in oncotic pressure would be 23.7 mmHg (1.23 × 19.3).

When the plasma protein concentration is half that of normal, 0.4 mmol/L, the discrepancy in diffusible ion concentration (calculated from the Donnan equilibrium) is only 0.11 mosm/L and, therefore, oncotic pressure is only 9.8 mmHg (0.51 × 19.3). On the other hand, doubling the protein concentration to 1.6 mmol/L increases the discrepancy in diffusible ion concentration to 1.64 mmHg, and the oncotic pressure will be (1.64 + 1.5) × 19.3 = 62.5 mmHg. The Donnan equilibrium explains why oncotic pressure is not linearly related to the plasma protein concentration (Table 1-1).

The oncotic pressure can also be calculated directly using an equation that combines the effect of the Donnan equilibrium and van't Hoff's equation:

$$\pi = RT\,(c + z^2c^2/4m_s),$$

where m_s is the molal concentration of diffusible ions, z the valency of protein, and c the molal concentration of protein. The average valency of plasma protein is 20

TABLE 1-1. Effect of Plasma Protein Concentration on Oncotic Pressure

PROTEIN CONCENTRATION (MOSM/L)*	0.4	0.8	1.2	1.6
DIFFERENCE IN DIFFUSIBLE IONS (MOSM/L)	0.11	0.43	0.95	1.64
TOTAL DIFFERENCE IN MOSM (MOSM/L)	0.51	1.23	2.15	3.24
ONCOTIC PRESSURE (MMHG)	9.8	23.7	41.5	62.5

* 7g/dL of protein is about equal to 0.8 mosm/L.

mEq/L (16 mEq for 0.8 mmol), and the molal concentration of diffusible ions is 140 mmol/L.

BODY FLUID VOLUME AND COMPOSITION

VOLUME

The treatment of many fluid and electrolyte disorders, particularly those involving depletion and excess of salt and water, requires at least a reasonable estimate of the amount of water in the body. Total body water (TBW) can be determined by dilution techniques using various substances including deuterium, tritium, and antipyrine. Total body water measured with antipyrine in hospitalized adults without demonstrable disturbances in fluid and electrolyte balances is about 54% of body weight. The relative water content of the body is much higher in infants and children and decreases progressively with aging. The water content also depends on the body content of fat; women and obese persons, because of their higher fat content, tend to have less water for a given weight.

A useful shortcut for the calculation of total body water, using the fact that 54% of body weight in kilograms is body water, and 1 kg is 2.2 lb is as follows:

$$\frac{\text{Body weight (lbs)}}{4} = \text{total body water (L)}.$$

For an obese subject, subtract 10% from the calculated body water, and for a lean person add 10%. For a very obese person, subtract 20%. Women have about 10% less body water than men for the same body weight. The above calculation applies only to individuals who are in a normal state of water balance. In the edematous state the margin for error could be very great because gross fluid retention, for example, of as much as 100% of body water is still compatible with life. However, in dehydrated states, the margin for error is limited by the fact that gross fluid losses are lethal. If an individual is severely dehydrated, his body water may be estimated by subtracting 10% from the calculated amount.

The intracellular volume is estimated as the difference between total body water and extracellular volume, but extracellular volume must be measured directly. Whereas measurement of total body water by the dilution technique is simple and the results are reproducible, the measurement of extracellular fluid poses a great

deal of technical difficulty, because no material has been found that distributes evenly and exclusively in the extracellular fluid. Some of the markers used for measurement of extracellular fluid volume, such as sodium, chloride, and bromide, penetrate the cells to varying degrees. Conversely, other markers, such as mannitol, inulin, and sucrose, do not penetrate certain parts of the extracellular fluid. Thus, depending on the type of marker used, the extracellular fluid volume could vary from 27% to 53% of total body water.

Extracellular volume, measured from the space of distribution of chloride and expressed as a percentage of total body water, varies from 42% to 53%. The values tend to be greater in older subjects and in women than in younger subjects and in men. Extracellular volumes measured from the space of distribution of inulin and sulfate are much smaller, on the order of 30% to 33% of total body water. For clinical application, a value of 40% of total body water will be considered to represent extracellular volume. Extracellular volume is further divided into three fractions: interstitial volume (28% of total body water), plasma volume (8%), and transcellular water volume (4%). Transcellular water includes luminal fluid of the gastrointestinal tract, the fluids of the central nervous system, and fluid in the eye as well as the lubricating fluids at serous surfaces (Table 1-2).

COMPOSITION OF FLUIDS

Extracellular Composition

The concentrations of electrolytes in plasma are easily measured and their values are well known. Concentrations of ions increase by about 7% when the concentrations are expressed in plasma water because about 7% of plasma is solids. Thus, plasma sodium is 140 mEq/L, but the concentration in plasma water is 151 mEg/L. The concentrations of electrolytes in interstitial fluid are different from those in the plasma because of the effect of the Donnan equilibrium. As predicted in Table 1-1, the concentrations of diffusible cations are higher in plasma water than in interstitial water by about 3%, whereas the concentrations of diffusible anions are lower in the plasma than in the interstitium by the same percentage. The concentrations of calcium and magnesium in the interstitial fluid are lower than the values predicted by the Donnan equilibrium, because these ions are partially protein-bound, and the interstitial protein concentration is lower than that of plasma.

TABLE 1-2. Volumes of Body Fluid Compartments*

Intracellular volume	24 L (60%)
Extracellular volume	16.0 L (40%)
Interstitial volume	11.2 L (28%)
Plasma volume	3.2 L (8%)
Transcellular volume	1.6 L (4%)

* A normal man weighing 73 kg with 40 L of total body water is used as a model.