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Bruce M.Koeppen
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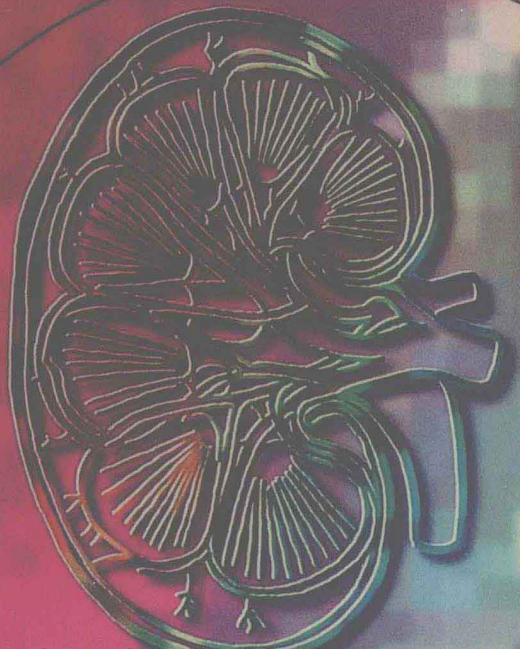
肾生理学

Renal Physiology

THIRD EDITION



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Renal Physiology

Third Edition

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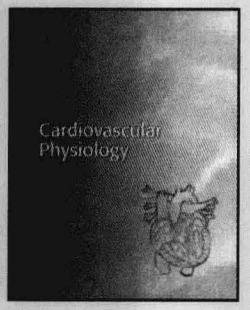

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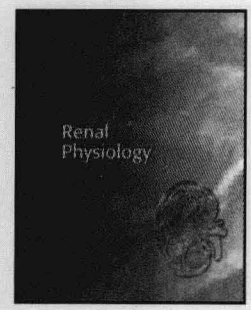

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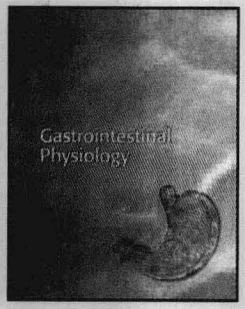

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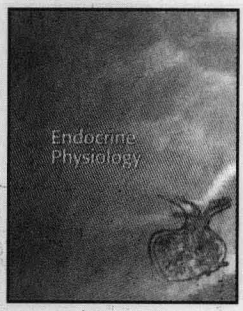

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Preface

IN THIS, THE THIRD EDITION, WE HAVE maintained our original goal to write a textbook that provides the basics of renal physiology for the health professions student studying the kidney for the first time. In addition to updating all chapters, we have added new emphasis to several topics, including genetic diseases of the kidneys. In addition to two multiple-choice examinations, clinical cases were included to assist the student in integrating the material. Answers are provided for student self-evaluation. Finally, we have emphasized the clinical relevance of important physiologic principles in boxes throughout the text. For every addition that we made, we deleted material where appropriate. Thus the third edition is similar to the first in length.

To the instructor: This book is intended to provide students in the biomedical and health sciences with a basic understanding of the workings of the kidneys. We feel it is better for the student at this stage to master a few central concepts and ideas rather than assimilate a large array of facts. Consequently, this book is designed to teach the important aspects and fundamental concepts of normal renal function. We have emphasized clarity and conciseness in presenting the material. To accomplish this goal, we have been selective in the material included. The broader field of nephrology, with its current and future frontiers, is better learned at a later time and only after the "big picture" has been well established. For clarity and simplicity, we have made statements as assertions of fact, even though we recognize that not all aspects of a particular problem have been resolved.

To the student: As an aid to learning this material, each chapter includes a listing of objectives that reflect the fundamental concepts to be mastered. At the end of each chapter, we have provided a summary and a listing of key words and concepts that should serve as a checklist while working through the chapter. We have also provided a series of self-study questions.

These questions review the central principles to be mastered. Because these questions are learning tools, answers and explanations are provided in an appendix. Two multiple-choice examinations and comprehensive clinical cases are included in another appendix. We recommend working through these tests and clinical cases only after completing the book. In this way, they can serve to indicate where additional work or review is required.

We have provided an updated annotated bibliography of selected books, monographs, and papers. This highly selective bibliography is intended to provide the next step in the study of the kidney; it is a place to begin to add details to the subjects presented here and a resource for exploring other aspects of the kidney not treated in this book.

We encourage all who use this book to send us your comments and suggestions. Please let us know what we've done right, as well as what needs improvement.

Acknowledgments: We thank our students at the University of Connecticut Medical School and Dartmouth Medical School and our colleagues, who made helpful comments and suggestions on the first two editions of this book. Most of their suggestions and comments have been incorporated into this edition. We thank Drs. Nancy Adams, William Arendshorst, Geza Fejes-Toth, Peter Friedman, Dan Henry, Andre Kaplan, John Mills, David Pollock, Brian Remillard, and Cynthia Short, who read early versions of this and previous editions and provided excellent criticism and suggestions. A special thanks is also given to Dr. Jay Bucci for his help in preparing the multiple choice examinations. Finally, we thank William Schmitt and his staff at Mosby for their support and commitment to quality and Karen Majeski for her help in preparing the manuscript.

Bruce M. Koeppen
Bruce A. Stanton

Introduction to the Kidney

"The kidney presents in the highest degree the phenomenon of sensibility, the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism; a power of adaptation which almost gives one the idea that its component parts must be endowed with intelligence."

E. Starling - 1909

AS STARLING RECOGNIZED, THE KIDNEYS are viewed more appropriately as regulatory, rather than excretory, organs. However, it is clear that the excretory function of the kidneys is central to their ability to regulate the composition and volume of the body fluids.

In this book, various aspects of renal physiology are explored. Emphasis is placed on providing insight and understanding into the major functions of the kidneys, which are as follows:

- Regulation of body fluid osmolality and volume
- Regulation of electrolyte balance
- Regulation of acid-base balance
- Excretion of metabolic products and foreign substances
- Production and secretion of hormones

In the chapters that follow, these aspects of renal function are considered in detail. However, in order to provide a broad perspective and overview, they are briefly described here.

Regulation of body fluid osmolality and volume (Chapters 1, 5, and 6): The kidneys are critical components of the system involved in the control of both the osmolality and volume of the body fluids. The control of body fluid osmolality is important for the maintenance of normal cell volume in virtually all tissues of the body, and control of the volume of body fluids is necessary for normal function of the cardiovascular system. The kidneys, working in an integrated fashion with components of the cardiovascular and central nervous systems, accomplish these tasks by regulating the excretion of water and NaCl.

Regulation of electrolyte balance (Chapters 4, 5, 6, 7, 8, and 9): The kidneys play an essential role in regulating the amount of several important inorganic ions in the body, including sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), hydrogen ion (H^+), calcium (Ca^{++}), and phosphate (Pi). The kidneys also contribute to the maintenance of organic ion balance.

For example, the excretion of many of the intermediates of the Krebs cycle (e.g., citrate, succinate) is controlled by the kidneys. In order to maintain appropriate balance the excretion of any one of these electrolytes must be balanced to the daily intake. If intake exceeds excretion, the amount of a particular electrolyte in the body increases. Conversely, if excretion exceeds intake, the amount decreases. For many of these electrolytes the kidneys are the sole or primary route for excretion from the body. Thus, electrolyte balance is achieved by carefully matching daily excretion by the kidneys with daily intake.

Regulation of acid-base balance (Chapter 8): Many of the metabolic functions of the body are exquisitely sensitive to pH. Thus the pH of the body fluids must be maintained within very narrow limits. This is accomplished by buffers within the body fluids and the coordinated action of the lungs and kidneys. The importance of the kidneys in acid-base balance is underscored by the fact that acid accumulates in the body fluids of individuals with reduced renal function.

Excretion of metabolic products and foreign substances (Chapters 3 and 4): The kidneys excrete a number of end products of metabolism that are no longer needed by the body. These so-called waste products include urea (from amino acids), uric acid (from nucleic acids), creatinine (from muscle creatine), end products of hemoglobin metabolism, and metabolites of hormones. These substances are eliminated from the body by the kidneys at a rate that matches their production. Thus their concentrations within the body fluids are maintained at a constant level. The kidneys also represent an important route for elimination of foreign substances from the body, including drugs, pesticides, and other chemicals ingested in the food. When kidney function is compromised, metabolic waste products and foreign substances accumulate in the body because their excretion in the urine decreases.

Production and secretion of hormones (Chapters 6 and 9): The kidneys are important endocrine organs, producing and secreting renin, calcitriol (1,25-dihydroxyvitamin D_3), and erythropoietin. Although renin is a proteolytic enzyme and not a hormone, it activates the renin-angiotensin-aldosterone system, which is important in regulating blood pressure, as well as sodium and potassium balance. Calcitriol is necessary for normal reabsorption of Ca^{++} by the gastrointestinal tract and for its deposition in bone. With renal disease the ability of the kidneys to produce calcitriol is impaired, and levels of this hormone are reduced. As a result, Ca^{++} reabsorption by the intestine is decreased. This reduced intestinal Ca^{++} reabsorption contributes to the abnormalities in bone formation seen in patients with chronic renal disease. Erythropoietin stimulates red blood cell formation by the bone marrow. With many kidney diseases, erythropoietin production and secretion is reduced, which by decreasing erythrocyte production is a causal factor in the anemia seen in chronic renal failure.

In the following chapters various aspects of these important renal functions are considered. Where information is available, these functions are considered at several levels of organization: whole kidney, single nephron, individual tubular cell, cell membrane, and transport protein.

Adaptation to nephron loss (Chapter 11): An overriding theme of this book is the ability of the kidneys to respond to the homeostatic needs of the individual. The degree to which renal function can be regulated to meet these needs is truly impressive. For example, urine volume can vary from 0.5 to 18 L/day. However, the limits of renal function are infrequently reached in healthy individuals. It is useful to study diseased kidneys to appreciate the extremes to which kidneys can function. Consequently a brief discussion of the physiologic adaptation to nephron loss is presented. This section emphasizes the ability of the kidneys to maintain fluid, electrolyte, and acid-base balance as the number of functioning nephrons is reduced by disease processes.

Contents

CHAPTER 1

Physiology of Body Fluids

Objectives

Upon completion of this chapter, the student should be able to answer the following questions:

1. How do the body fluid compartments differ with respect to their volumes and ionic compositions?
2. What are the driving forces responsible for movement of water across cell membranes and the capillary wall?
3. How do the volumes of the intracellular and extracellular fluid compartments change under various pathophysiologic conditions?

In addition, the student should be able to define and understand the following properties of physiologically important solutions and fluids:

1. Molarity and equivalence
2. Osmotic pressure
3. Osmolarity and osmolality
4. Oncotic pressure
5. Tonicity

ONE OF THE MAJOR FUNCTIONS OF THE kidneys is to maintain the volume and composition of the body fluids constant despite wide variation in the daily intake of water and solutes. This chapter discusses the volume and composition of the body fluids to provide a background for the study of the kidneys as regulatory organs. Some of the basic principles, terminology, and concepts related to the properties of solutes in solution are also reviewed.

■ PHYSICOCHEMICAL PROPERTIES OF ELECTROLYTE SOLUTIONS

Molarity and Equivalence

The amount of a substance dissolved in a solution (i.e., its concentration) is expressed either in terms of **molarity** or **equivalence.** *Molarity* is the amount of a substance relative to its molecular weight. For example, glucose has a molecular weight of 180 g/mol. If 1 L of water contains 1 g of glucose, the molarity of

this glucose solution would be determined as follows:

$$\frac{1\ \text{g/L}}{180\ \text{g/mol}} = 0.0056\ \text{mol/L or } 5.6\ \text{mmol/L} \quad (1\text{-}1)$$

For uncharged molecules such as glucose and urea, concentrations in the body fluids are usually expressed in terms of molarity.[1] Because many of the substances of biologic interest are present at very low concentrations, units are more commonly expressed in the millimolar range (mmol/L or mM).

The concentration of solutes, which normally dissociate into more than one particle when dissolved in solution (e.g., NaCl), is usually expressed in terms of equivalence. *Equivalence* refers to the stoichiometry of the interaction between cations and anions and is determined by the valence of these ions. For example, consider a 1-L solution containing 9 g of NaCl (molecular weight = 58.4 g/mol). The molarity of this solution is 154 mmol/L. Because NaCl dissociates into Na^+ and Cl^- ions, and assuming complete dissociation, this solution contains 154 mmol/L of Na^+ and 154 mmol/L of Cl^-. Because the valence of these ions is 1, these concentrations can also be expressed as milliequivalents (mEq) of the ion per liter (i.e., 154 mEq/L for Na^+ and Cl^-, respectively).

For univalent ions, such as Na^+ and Cl^-, concentrations expressed in terms of molarity and equivalence are identical. However, this is not true for ions that have valences greater than 1. Accordingly, the concentration of Ca^{++} (molecular weight = 40.1 g/mol and valence = 2) in a 1-L solution containing 0.1 g of this ion could be expressed as follows:

$$\frac{0.1\ \text{g/L}}{40.1\ \text{g/mol}} = 2.5\ \text{mmol/L} \quad (1\text{-}2)$$
$$= 2.5\ \text{mmol/L} \times 2\ \text{mEq/mmol} = 5\ \text{mEq/L}$$

Although some exceptions exist, it is customary to express concentrations of ions in milliequivalents per liter.

Osmosis and Osmotic Pressure

The movement of water across cell membranes occurs by the process of **osmosis.** The driving force for this movement is the osmotic pressure difference across the cell membrane. Figure 1-1 illustrates the concept of osmosis and the measurement of the osmotic pressure of a solution.

Compartments A and B are separated by a semipermeable membrane (i.e., the membrane is highly permeable to water but impermeable to solute). Compartment A contains a solute, whereas compartment B contains only distilled water. Over time, water will move by osmosis from compartment B to compartment A.[2] This will raise the level of fluid in compartment A and decrease the level in compartment B. At equilibrium the hydrostatic pressure exerted by the column of water (h) will stop the movement of water from compartment B to A. This pressure will be equal and opposite to the osmotic pressure exerted by the solute particles in compartment A.

1 The units used to express the concentrations of substances in various body fluids differ among laboratories. The system of international units (SI) is used in most countries and in most scientific and medical journals in the United States. Despite this convention, traditional units are still widely used. For urea and glucose, the traditional units of concentration are mg/dl (i.e., milligrams per deciliter or 100 ml), whereas the SI units are mmol/L. Similarly, electrolyte concentrations are traditionally expressed as mEq/L, whereas the SI units are mmol/L (see Appendix B).

2 This water movement is driven by the concentration gradient for water. Because of the presence of solute particles in compartment A, its concentration of water is less than that in compartment B. Consequently, water moves across the semipermeable membrane from compartment B to compartment A down its gradient.

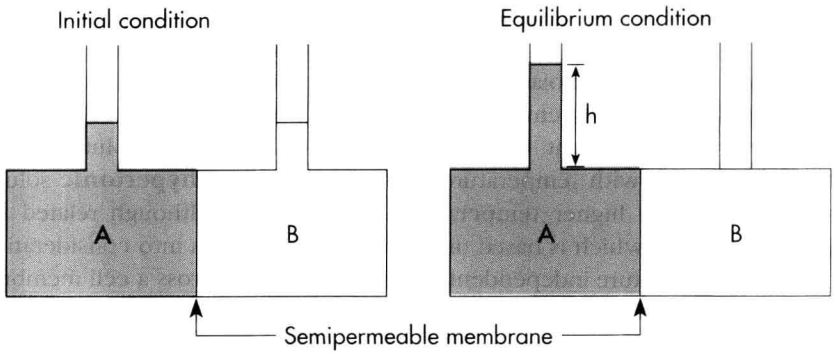

Figure 1-1 ■ Schematic representation of osmotic water movement and the generation of an osmotic pressure. The solute particles in compartment *A* cause water to move by osmosis from compartment *B* across the semipermeable membrane into compartment *A*. The water column in compartment A will rise until the hydrostatic pressure generated by the water column *(h)* stops the flow of water from compartment *B* into compartment *A*. This hydrostatic pressure is equal to the osmotic pressure generated by the solution in compartment *A*.

Osmotic pressure is determined solely by the number of solute particles in that solution. It is not dependent on such factors as the size of the solute particles, their mass, or their chemical nature (e.g., valence). Osmotic pressure (π), measured in atmospheres (atm), is calculated by **van't Hoff's law** as follows:

$$\pi = nCRT \qquad (1\text{-}3)$$

where:

n = Number of dissociable particles per molecule
C = Total solute concentration
R = Gas constant
T = Temperature in degrees Kelvin (°K)

For a molecule that does not dissociate in water, such as glucose or urea, a solution containing 1 mmol/L of this solute at 37° C can exert an osmotic pressure of 2.54×10^{-2} atm as calculated by equation 1-3 using the following values:

$n = 1$
$C = 0.001$ mol/L
$R = 0.082$ atm L/mol °K
$T = 310$ °K

Because 1 atm equals 760 mm Hg at sea level, π for this solution can also be expressed as 19.3 mm Hg.

Alternatively, osmotic pressure is expressed in terms of osmolarity (see the following). Thus a solution containing 1 mmol/L of solute particles exerts an osmotic pressure of 1 mOsm/L.

For substances that dissociate in a solution, n of equation 1-3 will have a value other than 1. For example, a 150 mmol/L solution of NaCl has an osmolarity of 300 mOsm/L because each molecule of NaCl dissociates into a Na^+ and a Cl^- ion (i.e., $n = 2$). If dissociation of a substance into its component ions is not complete, n will not be an integer. Accordingly, osmolarity for any solution can be calculated as follows:

$$\text{Osmolarity} = \text{Concentration} \times \#\ \text{Dissociable particles} \qquad (1\text{-}4)$$

$$\text{mOsm/L} = \text{mmol/L} \times \#\ \text{Particles/molecule}$$

Osmolarity and Osmolality

Osmolarity and **osmolality** are often confused and incorrectly interchanged. *Osmolarity* refers to the number of solute particles per 1 L of sol-

vent, whereas *osmolality* is the number of solute particles in 1 kg of solvent. For dilute solutions, the difference between osmolarity and osmolality is insignificant. Measurements of osmolarity are temperature dependent because the volume of solvent varies with temperature (i.e., the volume is larger at higher temperatures). In contrast, osmolality, which is based on the mass of solvent, is temperature independent. For this reason, *osmolality* is the preferred term for biologic systems and is used throughout this and subsequent chapters. Osmolality of biologic fluid, with water as the solvent, has the units of Osm/kg H_2O. Because of the dilute nature of physiologic solutions, osmolalities are expressed as milliosmoles per kilogram water (mOsm/kg H_2O).

Table 1-1 shows the relationship between molecular weight, equivalence, and osmoles for a number of physiologically significant solutes.

Tonicity

The **tonicity** of a solution is related to its effect on the volume of a cell. Solutions that do not change the volume of a cell are said to be **isotonic.** A **hypotonic** solution causes a cell to swell, whereas a **hypertonic** solution causes a cell to shrink. Although related to osmolality, tonicity also takes into consideration the ability of the solute to cross a cell membrane.

Consider two solutions: a 300-mmol/L solution of sucrose and a 300-mmol/L solution of urea. Both solutions have an osmolality of 300 mOsm/kg H_2O and are therefore isosmotic. When red blood cells, which for the purpose of this illustration also have an intracellular fluid osmolality of 300 mOsm/kg H_2O, are placed in the two solutions, those in the sucrose solution maintain their normal volume, whereas those placed in urea swell and eventually burst. Thus the sucrose solution is isotonic, and the urea

TABLE 1-1

Units of measurement for physiologically significant substances

Substance	Atomic/molecular weight	Equivalents/mol	Osmoles/mol
Na^+	23.0	1	1
K^+	39.1	1	1
Cl^-	35.4	1	1
HCO_3^-	61.0	1	1
Ca^{++}	40.1	2	1
P_i	95.0	3	1
NH_4^+	18.0	1	1
NaCl	58.4	2*	2†
$CaCl_2$	111	4‡	3
Glucose	180	—	1
Urea	60	—	1

*One equivalent each for Na^+ and Cl^-.

†NaCl does not dissociate completely in solution. The actual osmoles/mol is 1.88. However, for simplicity, a value of 2 is often used.

‡Ca^{++} contributes two equivalents, as do the Cl^- ions.

solution is hypotonic. The differential effect of these solutions on red cell volume is related to the permeability of the plasma membrane to sucrose and urea. The red cell membrane is highly permeable to urea but impermeable to sucrose.

To exert an osmotic pressure across a membrane, a solute must not permeate that membrane. Because the red cell membrane is impermeable to sucrose, sucrose exerts an osmotic pressure equal and opposite to the osmotic pressure generated by the contents of the red cell (in this case, 300 mOsm/kg H_2O). In contrast, urea is readily able to cross the red blood cell membrane, and it cannot exert an osmotic pressure to balance that generated by the intracellular solutes of the red blood cell.[3] Consequently, sucrose is termed an ***effective osmole,*** whereas urea is referred to as an ***ineffective osmole.***

To take into account the effect on osmotic pressure of a solute's ability to permeate the membrane, it is necessary to rewrite equation 1-3 as follows:

$$\pi = \sigma(nCRT) \qquad (1\text{-}5)$$

where σ is the ***reflection coefficient*** or ***osmotic coefficient*** and is a measure of the relative ability of the solute to cross a cell membrane.

For a solute that can freely cross the cell membrane, such as urea, $\sigma = 0$, and no effective osmotic pressure is exerted. A substance of this type is said to be an ineffective osmole. In contrast, $\sigma = 1$ for a solute that cannot cross the cell membrane. Such a substance is said to be an effective osmole. Many solutes are neither completely able nor completely unable to cross cell membranes (i.e., $0 < \sigma < 1$) and generate an osmotic pressure that is only a fraction of what is expected from the total solute concentration.

Oncotic Pressure

Oncotic pressure is the osmotic pressure generated by large molecules (especially proteins) in solution. As illustrated in Figure 1-2, the magnitude of the osmotic pressure generated by a solution of protein does not conform to van't Hoff's law. The cause of this anomalous relationship between protein concentration and osmotic pressure is not completely understood but appears to be related to the size and shape of the molecule. For example, the correlation to van't Hoff's law is more precise with small, globular proteins than with larger protein molecules.

The oncotic pressure exerted by proteins in human plasma has a normal value of approximately 26 to 28 mm Hg. Although this pressure appears to be small when considered in terms of osmotic pressure (28 mm Hg $\approx$ 1.4 mOsm/kg H_2O), it is an important force involved in fluid movement across capillaries (details on this topic are presented in the following section of fluid exchange between body fluid compartments).

Specific Gravity

The total solute concentration in a solution can also be measured as **specific gravity.** *Specific gravity* is defined as the weight of a volume of solution divided by the weight of an equal volume of distilled water. Thus the specific gravity of distilled water is 1. Because biologic fluids contain a number of different substances, their specific gravities are greater than 1. For example, normal human plasma has a specific gravity in the range of 1.008 to 1.010.

3 Urea traverses the plasma membrane of red blood cells via a specific transport protein, with the driving force for movement being the urea concentration gradient. Thus, when the red cell is placed in the urea solution, urea enters the cell down its concentration gradient.