# Renal Pathophysiology

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# Series Preface

It has come to be generally appreciated that knowledge concerning the pathophysiology of organ dysfunction serves as the basis for our understanding of the underlying mechanisms of disease. The phenomenal growth of pathophysiology as a discipline during the past ten years and its efficacy in medical education have prompted the preparation of the Wiley Pathophysiology Series.

Until recently, the traditional method of instructing first- and second-year medical students has been to teach the basic sciences including pharmacology and biochemistry separately. Today, however, an increasing number of medical schools have come to favor a multidisciplinary course of study where the pathophysiology of each organ system is examined and dealt with in its entirety. It has been found that this provides medical students with a firm base of knowledge concerning cellular biology and basic science and their relevance to the practice of medicine. The purpose of this series is to offer an accompaniment to such a curriculum that is both thorough and up-to-date.

The first book in the series, *Pathophysiology of Respiration* deals with the disordered function of the respiratory system. Dr. Kryger and his colleagues at the Universi of Manitoba Medical School present a concise multidisciplinary treatment of the subject that touches on all aspects of the altered performance of the diseased lung. It is felt that this work adds a valuable perspective to current medical knowledge, and it is hoped that teachers and practitioners of medicine as well as second-year students will find it stimulating and useful.

The unfailing support and courtesy of the staff of John Wiley & Sons is gratefully acknowledged.

Neville Bittar, M.D.
University of Wisconsin, Madison

# Preface

In our contacts with second-year medical students we have often been impressed by their ability to learn large amounts of detailed material in a short time—a talent that serves them well in the early years of their medical education. When we deal with more advanced students and medical residents, however, we are sometimes chagrined to discover that some fundamental principles of renal physiology and disease have escaped them. All of us have difficulty remembering many of the things we have learned. But perhaps a part of the problem here is that the original learning was focused too much on numerous facts to be remembered and not enough on basic concepts.

This book attempts to address that problem by emphasizing the basic ideas in current knowledge of renal physiology and disease. We have presented these ideas in an informal style that we hope is lucid, interesting, and even entertaining at times. Of course, there is far more to be learned about renal physiology and disease than what we have included. It is our hope that at least some readers will become sufficiently interested in the subject to pursue it elsewhere in more detail. We have not attempted to provide references to original experimental work, but we have listed at the end of each chapter some general review articles or other sources where the student may find more information and references.

A more detailed and scholarly approach than ours may also be found in a number of other texts. Among these, we should mention especially the classic by Robert F. Pitts, *Physiology of the Kidney and Body Fluids* (Chicago: Year Book Medical Publishers, 3rd ed., 1974), and two books by Heinz Valtin, *Renal Function* (Boston: Little, Brown, 1973) and *Renal Dysfunction* (Boston: Little, Brown, 1979). Our readers should also be aware of the big books—multiauthored volumes whose editors have succeeded in pulling together much of what is currently known about kidneys. The most available and recently published of these are *Strauss and Welt's Diseases of the Kidney*, edited by L. E. Earley and C. W. Gottschalk (Third Edition, Little, Brown & Co., 1979); *The Kidney*, edited by B. M. Brenner and F. C. Rector, Jr. (Second Edition, W. B. Saunders Co., 1981); *Nephrology*, edited by J. Hamburger, J. Crosnier, and J. P. Grünfeld (John Wiley & Sons, 1979); and *Pediatric Kidney Disease*, edited by C. M. Edelmann, Jr. (Little, Brown & Co., 1978). These volumes provide

abundant detail about almost everything renal and are therefore fine reference sources, but they may be difficult reading for a newcomer to the field.

Although this book deals primarily with pathology and normal and abnormal physiology, we have included some clinical material where it seemed appropriate, especially in the last six chapters. We have devoted two of those chapters to basic discussions of dialysis and renal transplantation because the management of patients with renal failure in the developed world now depends heavily on these methods; moreover, students often find themselves dealing with such patients without any introduction to the principles underlying their treatment.

We are enthusiastically in favor of sexual equality, but the English language does not provide a singular pronoun that refers to a person of either gender. "He or she" is too clumsy for repeated use, so we have reluctantly adopted the convention of using "he" for a person whose sex is not specified. We hope that our readers will interpret this as "he or she."

We would like to express our indebtedness to the many persons whose help and encouragement made this book possible. Many of our professional colleagues at the University of Wisconsin–Madison provided information, made suggestions, or reviewed chapters for us; they include Judith Blank, A. Vishnu Moorthy, Terry Oberley, David Simpson, Thomas Steele, Stuart Updike, Arvin Weinstein, and Sung-Feng Wen. Peter Burkholder did the electron microscopy on the renal biopsy specimens that are illustrated in the book. Michael Madden, a fellow in Nephrology, did most of the research and much of the writing in the chapters on dialysis and renal transplantation. He also reviewed several other chapters. A number of our second-year medical students (who were guinea pigs for some of these chapters) made useful suggestions and encouraged us to continue with this project.

Sue Reckinger and Avis Steele provided general secretarial support, and Linda Croxford, Lori Stalsberg, and especially Donna Davis did extensive typing, retyping, and correcting of the manuscript. Barbara Goodsit was responsible for almost all the original drawings. The diligence and patience of these women was greatly appreciated.

The preparation of this book placed unusual burdens on our wives, whose understanding support enabled us to continue. In addition, Carolyn Harrington spent many hours perusing the manuscript in order to help us eliminate nebulous writing. She also contributed one of the drawings.

*Avery R. Harrington*
*Stephen W. Zimmerman*

# Contents

# 1
# Some Basic Ideas

Not everyone who reads this book will start with the same background of information. So where should we begin? We would like this text to be understandable to everyone with a basic knowledge of physiology and biological chemistry, but we do not want to bore our readers with a recitation of what many of them already know. As a compromise we shall devote this chapter to a brief discussion of several concepts which are important to an understanding of subjects to be presented later. Those who are already well acquainted with this introductory material may choose to skip over it.

## BODY FLUID COMPARTMENTS

Water accounts for 50 to 70% of the human body by weight. The variation is explained largely by individual differences in body fat content. Adipose tissue may contribute heavily to body weight, but it contains only about 10% water. Muscle tissue, on the other hand, contains about 75% water. The finding that total body water averages 63% of body weight in men and 52% of body weight in women reflects the greater proportion of adipose tissue in women.

Body water is not found in one homogeneous fluid space. Rather, it is distributed among a number of *compartments,* as shown diagrammatically in Figure 1-1. These compartments differ from each other not only in their anatomic locations but also in the composition of their solutes and in their physiologic roles. We'll describe them very briefly.

### Intracellular Fluid (Cell Water)

Most of the water in the body—30 to 40% of total body weight—is within cells. The membranes confining this fluid appear to allow the free passage of water, but their vigorous transport mechanisms maintain a solute composition within the cells quite different from that on the outside. They do this by effectively excluding the most common solutes outside the cells—sodium and chloride—and sequestering other ions inside. Thus potassium and magnesium are

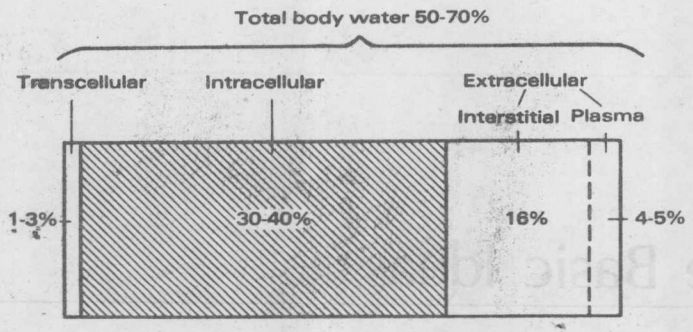


**Figure 1-1.** Diagrammatic representation of the body fluid compartments. Numbers show the size of each fluid space as a percentage of total body weight. There is considerable variation in these figures because of differences among individuals and among methods used to measure the compartments. We have included the fluid in bone matrix and connective tissue as a part of the interstitial fluid, but some authors prefer to treat them as separate subcompartments because they equilibrate slowly with the rest of the interstitial fluid.

numerically the most important cations dissolved in this cell water, while phosphates and proteins carry most of the anionic charges.

### Extracellular Fluid

Extracellular fluid is outside of cells and forms the environment around them. As already noted, the solute composition of this fluid is quite different from that within the cells; sodium is the dominant cation in the extracellular fluid, while chloride and bicarbonate are the major anions. There are two major subdivisions of the extracellular fluid—*plasma water* and *interstitial fluid.*

Plasma water (about 4.5% of body weight) is the water in which blood cells and platelets are suspended and plasma proteins dissolved—the liquid part of the blood, in short. Interstitial fluid (about 16% of body weight) lies outside the blood vessels and surrounds the cells. The only major difference between the solute composition of plasma water and interstitial fluid is the substantial concentration of protein found in plasma water. Since capillaries are quite permeable to the small ions that make up most of the solute in plasma water, the composition of these electrolytes is the same in plasma water and interstitial fluid except for small disparities due to the Donnan effect. The bulk distribution of fluid between plasma water and interstitial fluid is determined by Starling forces. The Donnan effect and Starling forces will both be described later in this chapter.

### Transcellular Fluid

Water amounting to 1 to 3% of body weight may be found distributed among a number of pools sequestered by secretory cells from other body fluid

compartments. Examples of such fluid collections are the cerebrospinal fluid, the aqueous and vitreous humors of the eye, and the secretions in the gastrointestinal lumen. By literal definition these transcellular fluid pools are a part of the extracellular fluid, since they represent body water not contained within cells. However, they differ from the main body of the extracellular fluid in function and solute composition as well as in location. When we describe the physiological role of the extracellular fluid in later chapters, we shall not consider transcellular water to be a part of it.

### Gains, Losses, and Shifts of Fluid

The division of body water into the compartments we have described is of more than academic importance. When fluid balance is upset, the different compartments may or may not be affected in the same way and to the same extent. The possible disturbances are numerous and complex, but a few simple examples here will serve for illustration.

We have already mentioned that water moves in and out of cells freely; this movement occurs passively in response to the concentration of solutes inside and outside of the cells, that is, *osmotic forces*. (See the section on osmolality in this chapter.) Ion pumps in cell membranes, especially sodium-potassium pumps, determine which solutes are kept in cells and which ones are evicted. Let's consider what happens to the volume of intracellular and extracellular fluid when water, sodium chloride or both together are added to the body.

The rectangle on the left side of Figure 1-2 represents the volumes of intracellular and extracellular fluid in a normal person. The rectangles on the right side of the figure show the effect of administering pure water, pure sodium chloride, or both together to this person. To keep our example simple we must assume that the kidneys and thirst mechanism are temporarily asleep and have not yet taken corrective measures.

If pure water is given to our subject, as shown in the top panel on the right,

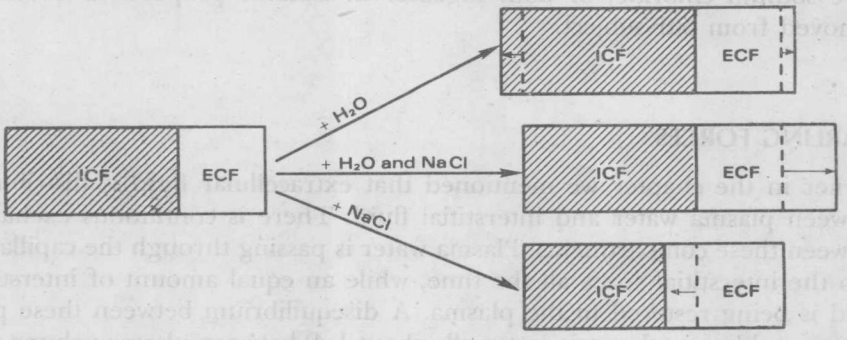


**Figure 1-2.** Changes in the size of intracellular and extracellular fluid compartments that would be caused by the addition of pure water, pure sodium chloride (NaCl), or both water and NaCl together in isotonic proportions. These figures assume that no compensatory adjustments have occurred.

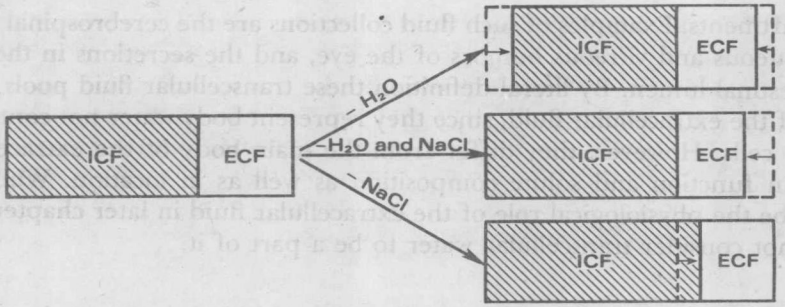


**Figure 1-3.** Changes in the size of intracellular and extracellular fluid compartments that result from removal of pure water, pure NaCl, or both water and NaCl together in isotonic proportions.

it will be distributed to both intracellular and extracellular fluid in roughly a 2:1 proportion, since the intracellular compartment is twice the size of the extracellular space; both compartments will be diluted.

If pure sodium chloride is given, it will be excluded from cells and confined to the extracellular space. The resulting increase of extracellular solute concentration will cause water to leave the cells, thus enlarging the extracellular space at the expense of intracellular fluid. This is shown by the lowest figure on the right. Though solute has been added to only the extracellular compartment here, osmolality will also rise within the cells because of their water loss.

If both water and sodium chloride are administered in the proportions found in normal plasma, the solute concentration in the body will not change, and there will be no shift of water into or out of cells. This is shown in the middle right-hand figure. Note, however, that all of the administered fluid is now added to the extracellular space alone.

Figure 1-3 depicts the reverse effects—what would happen if pure water, pure sodium chloride, or both together in isotonic proportions could be removed from our subject.

## STARLING FORCES

Earlier in the chapter we mentioned that extracellular fluid is distributed between plasma water and interstitial fluid. There is continuous exchange between these compartments. Plasma water is passing through the capillaries into the interstitial space all the time, while an equal amount of interstitial fluid is being restored to the plasma. A disequilibrium between these processes would upset the ratio (normally about 1:4) between plasma volume and the volume of interstitial fluid. Such a disturbance occurs in a number of disease states, but under normal circumstances the losses and gains of plasma

water and interstitial fluid are balanced with impressive precision. This is accomplished primarily by the operation of *Starling forces,* named after the English physiologist who suggested their role in 1896.

Stated very simply, Starling forces are hydrostatic pressure, which tends to force fluid out of capillaries, and the colloid osmotic force of dissolved proteins (often referred to as *oncotic pressure*), which tends to bring fluid back into the circulation. At the arterial end of a capillary, the blood pressure in the vessel is high enough to overcome the oncotic force of the plasma proteins. As a result, some plasma water and its small solutes (but not proteins) are forced out into the interstitial space. At the venous end of the capillary, however, the blood pressure has fallen to much lower levels. This allows the osmotic effect of plasma proteins to dominate the situation, with the result that interstitial fluid enters the capillary. A small amount of protein is found normally in the interstitial fluid, but its osmotic effect is usually balanced by the opposing hydrostatic pressure that is also present in the same compartment. These forces are shown diagrammatically in Figure 1-4.

The numbers in Figure 1-4 apply to an ordinary capillary, where the concentration of plasma proteins probably does not change significantly between the arterial and venous ends of the capillary. The same principles can be applied to other vascular beds where the situation is different. In glomerular capillaries, for instance, enough removal of fluid takes place to cause a significant rise in the intravascular protein concentrations. As we shall see, the resulting increase of oncotic pressure has an important effect on both glomerular filtration and the resorption of fluid from renal tubules.

Starling forces can also help us to understand certain disturbances of fluid distribution in the body. For instance, a low concentration of plasma albumin

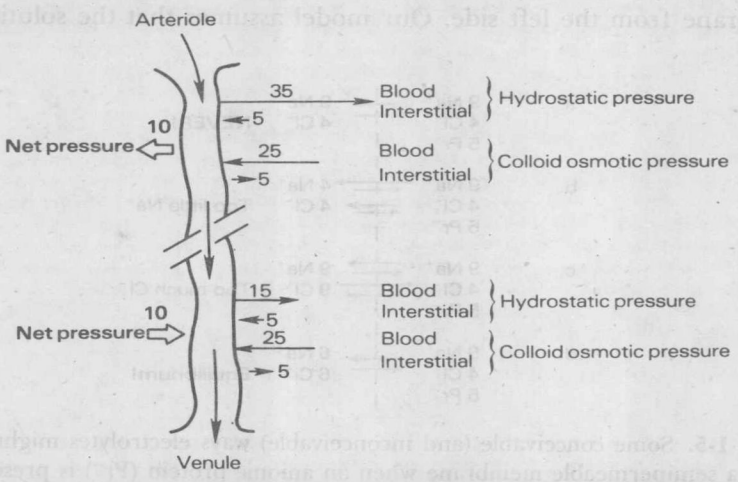


**Figure 1-4.** Starling forces in a muscle capillary. The figures show the approximate magnitude of each pressure in millimeters mercury.

will lessen oncotic pressure in the capillaries. Unless other factors can compensate for this reduction, there will be a net loss of plasma water into the interstitial space and formation of *edema* (see Chapter 4).

## THE DONNAN EQUILIBRIUM

In the preceding section we mentioned the direct osmotic effect exerted by the plasma proteins, which generally cannot pass through capillary walls into the interstitial space. These protein molecules in solution also have an effect on the distribution of small ions across capillary walls.

At the hydrogen-ion concentration found in blood, most plasma protein molecules are anions—that is, they have donated hydrogen ions and now carry a negative charge. Negative charges must be balanced by an equal number of positive charges, of course, and these are provided by small cations such as sodium. This accounts for the fact that there are more small cations (sodium, potassium, and others) in the plasma than small anions (chloride, bicarbonate, and others). To put it in different terms, we might say that some sodium ions are balanced by chloride and bicarbonate, while others are balanced by the anionic proteins.

Figure 1-5 examines what happens (and what doesn't happen) under these circumstances when ions diffuse across a membrane such as a capillary wall. On the left side of each panel we have represented a solution that contains sodium ($Na^+$), chloride ($Cl^-$), and protein ($Pr^-$) in the ionic proportions of 9:4:5. (These numbers don't reflect actual concentrations in the plasma, and they exaggerate the proportion of protein, but they make for easy arithmetic.) Other solutes have been omitted in the interest of simplicity. The solution on the right side of the membrane contains only the solutes that have crossed the membrane from the left side. Our model assumes that the solution in the

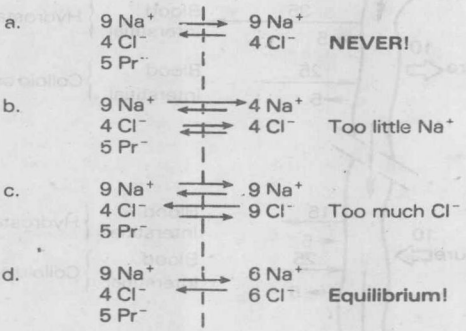


**Figure 1-5.** Some conceivable (and inconceivable) ways electrolytes might distribute across a semipermeable membrane when an anionic protein ($Pr^-$) is present on one side. As explained in the text, the situation in panel a is impossible, while the distributions in b and c are unstable. Only d represents an equilibrium.

compartment on the left is continuously replenished, so that its composition remains the same despite diffusion of sodium and chloride ions across the capillary wall.

In the first panel of the figure $Na^+$ and $Cl^-$ have crossed the membrane, leaving protein behind, until the concentrations of both are equal on both sides. This does not happen, however, because it violates electrochemical principles to have more cations than anions in the compartment on the right side.

Panel b shows the diffusion of $Na^+$ and $Cl^-$ in equal numbers until the concentration of $Cl^-$ is the same on both sides of the membrane. Chloride is now in equilibrium, but sodium is not, so the tendency for additional $Na^+$ to cross to the right side makes this an unstable situation.

If $Na^+$ and $Cl^-$ diffuse together until the concentration of $Na^+$ is equal on both sides, as shown in panel c, there will be much more $Cl^-$ on the right side of the membrane than the left side. This is not an equilibrium situation due to the tendency of $Cl^-$ to diffuse back to the left.

The chemical compromise that actually occurs is shown in the last panel. At equilibrium the compartment on the right side of the membrane will contain less $Na^+$ but more $Cl^-$ than the compartment on the left that contains the protein. Donnan demonstrated many years ago that equilibrium is reached when the product of the concentrations of a pair of diffusible ions (in this case $Na^+$ and $Cl^-$) is the same on both sides of the membrane. In our example, $9 \times 4 = 6 \times 6$.

A practical effect of this phenomenon is that the concentration of a monovalent cation such as $Na^+$ is about 5% less in the interstitial fluid than in plasma water, while that of a monovalent anion such as $Cl^-$ is about 5% greater in the interstitial fluid than in plasma. The same relationship holds for the solute content of glomerular filtrate. This difference in solute concentrations on the two sides of a capillary membrane is unimportant for most purposes but must be taken into account when precise measurements and calculations are being made, as in research studies.

An interesting corollary of the Donnan distribution is that the total concentration of *diffusible* ions is slightly greater on the side of the membrane where the nondiffusible protein is located. In terms of the example given in Figure 1-5, $9 + 4 > 6 + 6$. This increase in the total number of diffusible ions augments the direct osmotic effect of the plasma proteins.

## WHAT'S OSMOLALITY?

The movements of body water from one compartment to another are often governed by osmotic forces. These forces are determined by the concentrations of solute in the compartments.

When dissolved particles are present in a water solution, the activity or *escaping tendency* of the water molecules in that solution is reduced in propor-

tion to the concentration of dissolved particles. If pure water is placed on one side of a membrane that is permeable only to water molecules, and a solution of any solute in water is placed on the other side, water will escape from the pure-water compartment (where the activity of water is higher) to the compartment containing the solution (Fig. 1-6). If two different solutions are used, water will flow from the less concentrated to the more concentrated one. The ability of a solution to attract water, which reflects the reduced activity of its own water, depends upon its *osmolality.*

Osmolality is simply the concentration of solute molecules in a solvent, expressed as moles (or millimoles) of solute per kilogram of solvent.

You will recall that the molecular weight of any element or compound taken in grams is 1 g molecular weight of that substance, or 1 *mole.* For example, the molecular weight of glucose is 180. Therefore 180 g of glucose is 1 g molecular weight, or 1 mole, of glucose. Since the molecular weight of urea is 60, 1 mole of urea weighs 60 g. One mole of any substance contains the same number of molecules as 1 mole of any other substance: $6.02 \times 10^{23}$ molecules (Avogadro's number). A millimole is 0.001 mole.

One mole of molecules dissolved in 1 kg of water gives a 1 Osmolal solution.

*Examples*

180 g glucose in 1 kg of water is a 1 Osmolal solution.
60 g urea in 1 kg of water is a 1 Osmolal solution.

So osmolality is an expression of the concentration of dissolved molecules in a solution, regardless of their nature. If 180 g of glucose and 60 g of urea are dissolved in the same kg of water, we have a solution in which the concentration of glucose is 1 molal and that of urea is 1 molal, but the solution is a 2 Osmolal solution, 1 Osmole contributed by each solute.

When a compound dissociates in solution, osmolality depends upon the number of ions which each molecule produces.

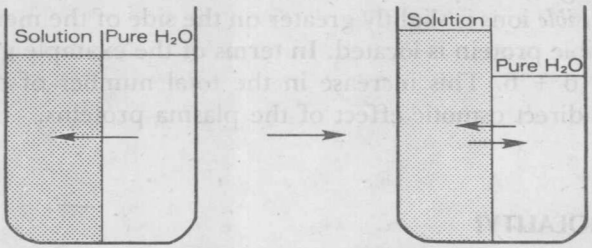


**Figure 1-6.** Molecules of water will tend to escape from a compartment containing pure water into one that contains water and solute, as shown on the left. The addition of water raises the level of the solute compartment until its hydrostatic pressure equals osmotic pressure. When that point is reached, water transfer across the dividing membrane becomes equal in both directions, as shown in the figure on the right.

*Example*

One mole of NaCl in 1 kg of water gives a solution that is approximately 2 Osmolal, since the NaCl dissociates almost completely to yield 1 mole of $Na^+$ ions and 1 mole of $Cl^-$ ions.

### Osmolality versus Osmolarity

Osmola*l*ity is the concentration of dissolved particles in solution expressed as moles of solute per *kilogram* of water. Osmola*r*ity is the concentration of dissolved particles in solution expressed as moles of solute per *liter* of the final solution.

If solute is added progressively to 1 kg (1 liter) of pure water, 1 kg of water continues to be present. But the total volume may no longer be 1 liter, since the volume of the solution may increase as solute is added. In concentrated solutions the difference between osmolality and osmolarity may be significant. In the dilute solutions commonly encountered in biology, the difference between osmolality and osmolarity is unimportant, but the use of osmolality is usually preferred for theoretical reasons.

Because body fluids usually have an osmolality less than 1 Osm/kg water, biologists commonly express osmolality in *milli*Osmoles per kilogram of water (1 mOsm = 0.001 Osm). The extracellular fluid of man normally has an osmolality of about 290 mOsm/kg water. Many other species have similar osmolalities.

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*Many textbooks of general physiology or biochemistry also include discussions of these subjects.*