RENAL PHYSIOLOGY

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Renal Physiology

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Preface

This book is intended as an introduction to renal physiology for first year medical students and graduate students. The emphasis is on regulation of kidney function. Modern research has clarified many of the mechanisms of regulation, and it is easier now than ever before to present this subject understandably. We believe this emphasis is important because regulatory processes are of natural interest to physiologists, and because disturbances of regulation are of great importance in diseases affecting the kidney and body fluids.

The most well-known early texts of renal physiology were written by Homer W. Smith and Robert F. Pitts. These revered figures established a format that has been used by most later authors, one in which each major constituent of the urine was followed separately along the nephron. Our teaching experience has convinced us that this is not the best approach to a discussion of regulation. Modern views of tubular function emphasize interactions among several transport processes, and suggest that most intrarenal regulation arises from these interactions. The plan we have followed therefore is to discuss each segment of the nephron in sequence, first outlining all the tubular transport processes and then showing how these multiple processes and their interactions generate local regulation.

The material presented here normally would be covered in two or three weeks of teaching; the organization and selection of topics is the same as we currently use in our teaching. A brief introduction to principles of membrane transport and to renal anatomy are included for the independent reader, and for courses taught primarily to graduate students. Student objectives are provided at the beginning of each chapter. Students appreciate having them because they make studying more efficient and are helpful for review. A problem set is provided at the end of Chapter 3, where the material is best illustrated by studying a numerical example.

We owe a debt to our students. Their reactions to our teaching have been an invaluable moderating influence, and an incessant pressure for clarity, organization, and cogency.

Acknowledgment

Nachman Brautbar, Associate Professor of Medicine, University of Southern California School of Medicine, contributed Chapter 11, "Calcium, Magnesium, and Phosphate Excretion".

Contents

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Chapter 1

Student Objectives

The student should:

1. Learn the major subdivisions of the body fluids and the approximate percentage of total body water in each.
2. Learn the concentrations of Na^+, K^+, Cl^-, and HCO_3^- in the extracellular and intracellular fluids.
3. Explain why the concentrations of inorganic cations are higher in plasma than in interstitial fluid, and why the reverse is true for the inorganic ions.
4. Explain why a change in the total amount of NaCl in the body affects primarily the extracellular fluid volume, and affects the osmolality of the body fluids only to a minor extent.
5. Describe the major modes of transport of materials within each of the major body fluid compartments, and also between them.

1

Body Fluid Compartments

This book is about body fluids and how the kidney regulates them. The urine contains materials the body must eliminate, and waste excretion is certainly an important function; our emphasis, however, is on the renal control of body fluids. This function is flexible, subtle, essential, and frequently involved in disease states.

To understand the importance of fluid regulation, it is useful to recall that virtually all cells in higher animals are specialized for certain functions and are unable to satisfy all of their needs by their own activity. Neurons in our visual cortex, for example, cannot digest disaccharides, exchange oxygen and carbon dioxide directly with the atmosphere, or regulate the plasma potassium concentration if dietary potassium intake falls. Some other organs must take care of these functions if we are to see. Controlling the strong electrolyte composition of the body fluids is the task of the kidney.

Cells are comprised mostly of water and are surrounded by water. Strong electrolytes are present in higher concentrations in these fluids than are any other materials. The concentrations of these electrolytes affect virtually every activity of virtually every cell, and proper function of any cell requires that these concentrations be regulated within narrow limits. The specialized functions of most cells arise in a fixed fluid environment. If that environment changes, different parts of each cell are affected differently, and integrated cell function becomes difficult or impossible. Moreover, the volumes of the body fluids are limited, and a change in the volume of a fluid therefore affects the concentration of all the solutes present in it. Hence another important aspect of regulating the body fluids, one also carried out by the kidney, is maintaining the volumes of the body fluids within narrow limits. The two regulatory tasks—volume and composition—are closely interrelated, as we will see in detail later.

Before we start to study the details of these regulatory processes, another point is worth noting, one made many years ago by Homer Smith, the father of modern renal physiology. Aquatic lower vertebrates use the external world as the dominant point of reference for the body fluids. The volume of the animal's body is usually so small in comparison to the volume of the body of water the animal lives in, and the composition of the external environment is usually so fixed, that renal mechanisms are under little evolutionary pressure to become adaptive. Renal function in such animals is thus quite primitive. As vertebrates became terrestrial, however, they were isolated from that point of reference. The aqueous environment was no

longer their whole world, but only the body itself. The disappearance of the external set point was a severe challenge, one that had to be met as vertebrates became separated from their watery environment. The most recent and advanced answer to that challenge is the mammalian kidney. Smith suggested that the evolution of the kidney was necessary before animals could be free to become fully terrestrial, as only then could they undergo the variety of experiences that led ultimately to the evolution of man. Hence we are what our kidneys have allowed us to become!

Because the emphasis of this book is to be the renal regulation of body fluids, we begin by describing the volumes and strong electrolyte composition of the various fluid compartments in normal human beings. Water accounts for about 60% of the body weight, so that in a 70-kg man total body water is 42 kg. The exact figure varies somewhat from person to person, the main variable being the mass of adipose tissue. In a given individual, however, there is little variability largely because of the kidney's efficiency as a regulator. Total body water is distributed among three compartments: extracellular, intracellular, and transcellular. Most of the fluid is in the first two compartments. The volumes of the extra- and intracellular compartments are closely regulated by a variety of mechanisms that involve the kidney, the brain, and a number of endocrine glands. These mechanisms are discussed in detail in this book.

Transcellular fluid is extracellular fluid in the lumen of the structures lined by epithelia. The volume of fluid in this compartment is highly variable because it depends on such functions as drinking, sweating, defecation, micturition, respiration, etc. The important point is that constancy of the volume of the intracellular and extracellular compartments is achieved by regulating the exchanges between transcellular and intracellular fluids in epithelia. This concept applies to regulation of body fluid volumes and to body fluid composition.

THE BODY FLUIDS

Measurement Methods

When considering how the kidney regulates fluid balance, it is useful to discuss the total volumes of these fluid compartments in the body. The total volume in each compartment is relatively large, but the physical dimensions of the spaces filled by these fluids are small and irregular. Measuring the various volumes requires some ingenuity. The techniques are worth a brief discussion because limitations of the methods determine how precisely the values can be specified. When we refer to some volume, it is a volume that we *measured*.

As a practical matter, the only nondestructive method for measuring the size of a body fluid compartment is a dilution technique. A material is chosen that is known to distribute at a uniform concentration through the compartment to be estimated, and a measured amount is injected. After a suitable delay to allow for mixing, the compartment fluid is sampled and the concentration of the injected material measured. Then, in principle, the volume *(V)* is given by $V = I/C$, where I is the mass

of material injected, and C is the concetration after equilibration. To measure total body water, for example, we can inject water labeled with deuterium or tritium. The problem is that once injected, most labels are removed by such processes as urine formation, sweating, respiration, metabolism, and so on, even though the volume of the space they are measuring does not change. To compensate for the changing concentration, it is customary to assume that the loss of the label is proportional to the concentration, so that the concentration decreases logarithmically. The time course of the label is shown in Fig. 1-1. The label is injected into some part of the body water, usually the blood plasma, at the time indicated by the arrow in Fig. 1-1. There is a sudden rise in concentration, and there may be an overshoot before the label distributes uniformly throughout the compartment. The concentration then enters a phase of decline that falls on a straight line if plotted semilogarithmically. If the concentration is measured at two or more points during this phase, and if the line is extrapolated back to the time of injection, we can read the concentration at zero time. This zero time value is the one used when calculating the volume. The various compartments measured this way are shown in Fig. 1-2A, together with an indication of how they are connected.

Body Fluid Volumes

Total Body Water

The labels used for measuring the volume of total body water are water labelled with deuterium or tritium, and antipyrine (a compound with a structure similar to

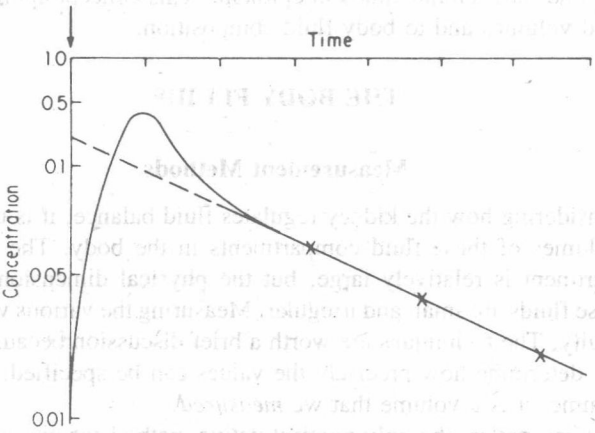

FIG. 1-1. Time course of a typical experiment designed to measure the volume of a fluid compartment by a dilution technique. The label is injected into a vein at the time indicated by the arrow. The concentration quickly rises in the blood, and then begins to fall as the label moves from blood into other fluid compartments. After an equilibration period the concentration in blood falls steadily, and the concentration that would have been present if the label had been equilibrated at the time of injection can be estimated by extrapolating the straight line back to the time of injection.

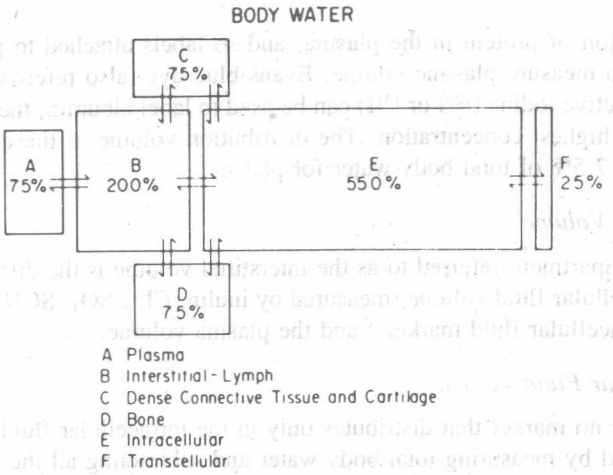

FIG. 1-2. This diagram shows how the various fluid compartments are connected and the relative volume of each compartment.

that of aspirin which crosses cell membranes rapidly and distributes in about the same volume as the two isotopes). These labels give a value of 60%, as mentioned previously. A more convenient way to follow changes in total body water is to measure body weight. Any measurable weight change over the course of a few hours or days is due primarily to loss or gain of fluids rather than proteins or fat.

Extracellular Fluid Volume

The extracellular fluid volume has several components, including plasma, interstitial fluid in tissues generally, and interstitial fluid in dense connective tissue, cartilage, and bone. There are several labels that distribute uniformly in plasma and ordinary interstitial fluid. These include sugars such as sucrose, raffinose, and inulin, a polyfructose with a molecular weight of 5,000 to 5,500 daltons. Other labels include Cl^-, $SO_4^=$, and SCN^-. All these labels cross capillaries and distribute at the same concentration in plasma and interstitial fluid. All give roughly the same value, with small systematic variations. The smaller labels enter cells to some extent, whereas the larger ones do not penetrate the smallest recesses of the extracellular fluid. Thus none is necessarily more correct than the others, and there is no absolute measure of this volume. Inulin is probably the label of choice. The interstitial space of dense connective tissue, cartilage, and bone is not readily entered by these labels, and estimates of interstitial volume are made by much more indirect means. A distinction is made among these three tissues because of the differences in the way they handle ions, as discussed below.

Plasma Volume

"Plasma volume" refers to the extracellular fluid contained within the circulatory system. A major difference between plasma and interstitial fluid is the much higher

concentration of protein in the plasma, and so labels attached to plasma proteins are used to measure plasma volume. Evans blue dye (also referred to as T-1824) and radioactive iodine (^{125}I or ^{131}I) can be used to label albumin, the plasma protein present in highest concentration. The distribution volume of these markers yields a value of 7.5% of total body water for plasma.

Interstitial Volume

The compartment referred to as the interstitial volume is the difference between the extracellular fluid volume (measured by inulin, Cl^-, SO_4, SCN^-, or any of the other extracellular fluid markers) and the plasma volume.

Intracellular Fluid Volume

There is no marker that distributes only in the intracellular fluid. Estimates can be obtained by measuring total body water and subtracting all the rest. Obviously this is not a very accurate method, but the major disorders of fluid volume regulation affect mainly the extracellular fluid volume, so the lack of good methods for measuring intracellular water is not a serious handicap to understanding diseases of fluid balance.

Strong Electrolyte Composition of Body Fluids

The body fluids contain an endless number of materials, either in solution or in suspension. Aside from water itself, the materials present in greatest abundance are a small number of strong electrolytes (Table 1-1). The strong electrolytes are dissolved in the various fluids, where they exert a variety of effects. The properties of these solutes that are of primary interest include their contribution to the osmotic pressure of the fluids, their function as substrates for membrane transport, and their contribution as determinants of pH of the various fluids.

TABLE 1-1. *Ionic composition of body fluids*

	Concentrations (mEq/L)			
Ion	Plasma	Plasma water	Interstitial fluid	Cell water (muscle)
Na^+	142	151	144	10
K^+	4	4.3	4	160
Ca^{++}	5	2.7	2.5	0
Mg^{++}	3	1.6	1.5	35
Cl^-	103	110	114	2
HCO_3^-	27	29	30.5	8
PO_4	2	2.1	2.2	
$SO_4^=$	1	1.1	1.2	
Organic phosphate	5	5.3	5.6	140
Protein	16		0	55

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The most abundant cation of the extracellular fluids is Na^+, and the major anions are Cl^- and HCO_3^-. Na^+ concentration is nearly uniform through the extracellular fluid, but it is consistently different between plasma and interstitial water. The difference has two sources, each related to the proteins present in plasma. First, about 95% of the volume of plasma is water, the rest being largely protein. Although measurements are usually made in plasma and not corrected for the volume occupied by proteins, the strong electrolytes are really dissolved only in water. Thus the concentrations of all strong electrolytes are 5% higher in plasma water than in plasma. However, if we compare the concentrations in plasma water with those in interstitial fluid, we still find small systematic differences that arise because the proteins present in plasma are anions. The need for electrical charge neutrality in each fluid compartment is absolute; to satisfy it, the concentration of small cations must exceed the concentration of small anions in the plasma water by an amount equal to the concentration of protein charge. Interstitial fluid has much less protein than plasma, so the concentrations of small cations and anions must be more nearly equal. The general classes of systems such as the plasma-interstitial fluid pair we have described are called Gibbs-Donnan systems, after the chemists who first analyzed them. Such systems have a membrane separating two electrolyte solutions. The membrane allows the passage of all but one of the ions, and this ion is usually not present in the same concentration in the two bathing solutions. The Gibbs-Donnan problem is important in discussions of how cells regulate volume, as we will see later. For the present, the important point to remember is that the higher concentration of protein in plasma causes slight differences in the concentrations of all smaller ions between plasma and interstitial fluid.

Most Na^+ in the body is simply dissolved in the extracellular fluid, although some is adsorbed on the surface of bone crystals. Bone has two Na^+ fractions: one that is an integral part of the hydroxyapatite crystal and does not exchange, and another that is adsorbed. This latter fraction is in chemical equilibrium with the extracellular fluid of bone. If an isotope of Na^+ is used to measure the mass of Na^+ in the body, the isotope exchanges readily with the adsorbed Na^+, which is therefore included in the estimate. If the extracellular concentration of Na^+ falls, Na^+ and some anions desorb from bone and enter extracellular fluid; the reverse is true when the concentration rises. Bone can therefore buffer the mass of Na^+ salts in the extracellular fluid. The distribution of Na^+ is shown in Fig. 1-3A.

The bulk of body K^+ is intracellular, where it is in simple solution and not bound or adsorbed to any significant extent. Potassium is the major cation of the cells. There is no K^+ storage in the body as is seen for Na^+ in bone matrix. Thus even a relatively small shift of K^+ from the cells into the extracellular fluid can cause a dramatic increase in plasma K^+, which depolarizes most cells. Depolarization of myocardial cells can lead to abnormalities of cardiac rhythms and death. This problem is particularly serious in patients with advanced renal disease because increased urinary excretion of K^+ is the only means the body has to deal with elevated plasma K^+ concentration.

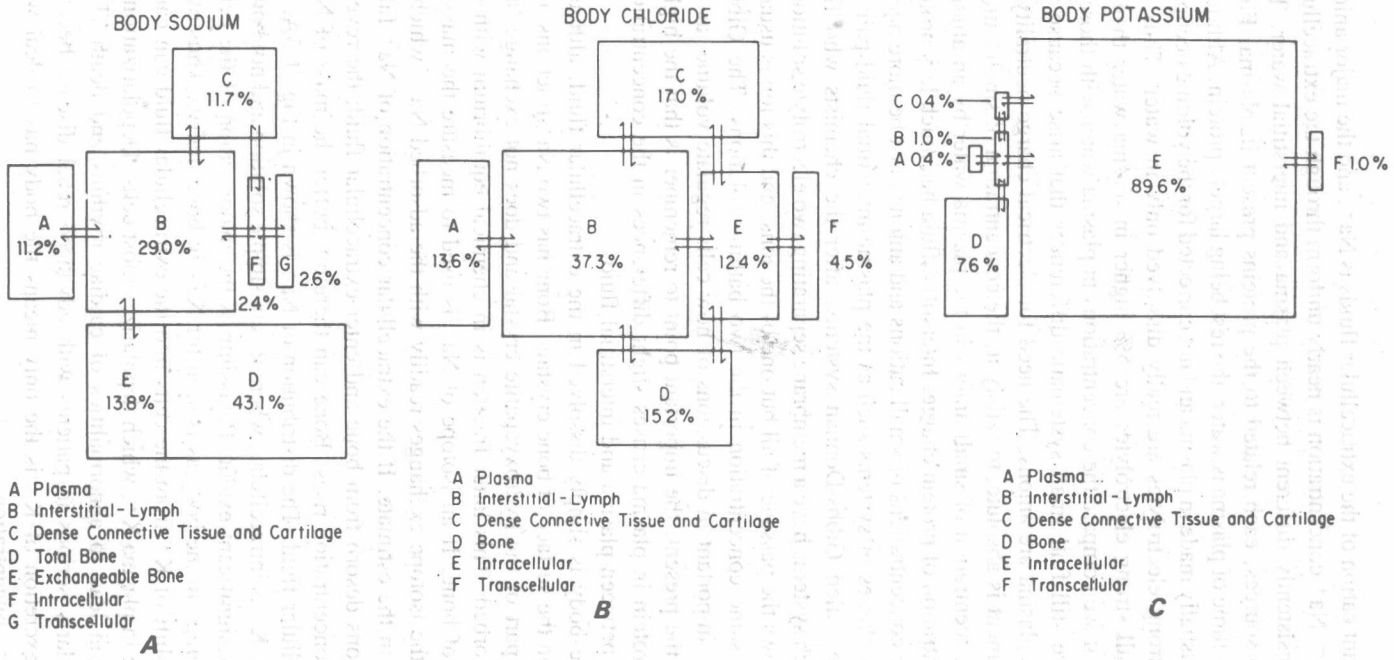

FIG. 1-3. **A:** Distribution of Na^+. The single largest compartment is in bone and is part of bone mineral. Almost all the rest is dissolved in extracellular fluid or adsorbed on bone. **B:** Distribution of Cl^- in the body. The major difference between the distributions of Cl^- and Na^+ is that Cl^- is not part of bone mineral. Most of the Cl^- is extracellular. **C:** Distribution of K^+, most of which is intracellular.

Finally, there is a difference in the Ca^{++} and Mg^{++} concentrations between plasma and interstitial fluid. The concentrations are higher in plasma because about one-half of the amount of each divalent cation is bound to protein and is not free in solution. Thus the major cause of the difference between plasma and interstitial concentrations is the higher concentration of protein in plasma. Regulation of these concentrations is discussed in Chapter 11.

GENERAL MODES OF TRANSPORT IN THE BODY

Figures 1-2 and 1-3 give a quantitatively accurate view of how water and the major electrolytes are distributed throughout the body, but the figures do not convey the dimensions of the various elements making up each compartment. The differences in these dimensions are great and lead to major differences in the mechanisms required to transport materials through the spaces. The three main modes we need to consider are convection, diffusion, and membrane transport.

Convection

Convection is the transport in bulk of some fluid with all of the formed elements and dissolved materials present in the transported fluid. Blood flow through the circulatory system and movement of transcellular fluid through hollow viscera lined with epithelium are the most important examples of convection. Convection is caused by a hydrostatic pressure difference between two ends of a tube. The fluid flows from a region of high pressure to one of lower pressure. Muscular contraction is usually responsible for generating the hydrostatic pressure difference in the body. The muscle for the circulatory system and kidney is the heart, whereas in other epithelia smooth muscle surrounding the lumen of the hollow organ usually creates the pressure difference. Convection is an efficient means for transporting fluid and everything dissolved or suspended in it rapidly over long distances.

Diffusion

Diffusion is the principal mode of material transport in the interstitial space and within cells. Unlike convection, where all materials move together in bulk, diffusion is a process that involves movement of individual ions or molecules. To understand the process of diffusion, imagine a tank filled with water containing some simple solute such as glucose. Imagine also that the glucose is present in higher concentration on the left side of the tank than on the right. Now let us examine a slab of fluid from the tank with sufficiently high resolution that we can observe the movement of individual glucose molecules (Fig. 1-4). Given enough time, each glucose molecule moves. If we could record the direction taken by all the molecules, we would find that there is no preferred direction, the movement of the molecules

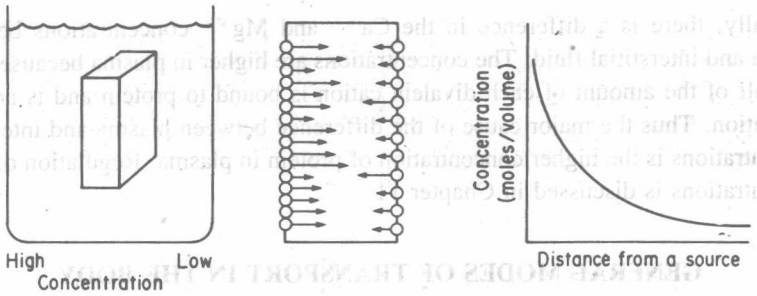

FIG. 1-4. Left: Glucose is dissolved in a large tank of water but is at higher concentration on the left. **Middle:** End-on view of the slab depicted in the middle of the tank. The circles are glucose molecules; the arrows indicate the distance each molecule moves into the slab over some arbitrary period of observation. **Right:** Glucose concentration as a function of distance from the region of highest concentration. The curve is taken at an instant in time. The concentration gradient at any distance from the origin is equal to the slope of the curve at that distance.

being random in space. This motion is known to be caused by the thermal energy of each molecule. Although the motion of each molecule is random and so cannot be predicted, an interesting property of the collection of molecules can be observed. At the left edge of the slab a certain number of molecules, moving randomly, will jump toward the right. On the right edge of the slab, a certain number of molecules, moving randomly, will jump to the left. However, because the total number of molecules jumping in all directions is greater on the left than on the right, there will be more molecules moving into the slab from the left than from the right. The net result is that glucose moves from left to right in proportion to the difference in concentrations. Because these solutions contain very large numbers of molecules, the net movement of material by diffusion has a regular character and exhibits none of the randomness that the underlying mechanism might lead you to expect. The law that governs material transport by diffusion, called Fick's law, is:

$$J = -DA\frac{dc}{dx}$$

where J is the flux of the material diffusing in units of mass/time, D is the diffusion coefficient in length^2/time, A is the cross-sectional area over which the diffusion occurs (length^2), c is the concentration in mass per unit volume, and x is the distance. This law simply states that when a material moves by diffusion it does so in proportion to the concentration gradient. The minus sign is needed to satisfy convention. D is a physical constant and must be positive; A also can have only positive values. The usual convention is to designate a flux that goes from left to right, i.e., from a lower value of x to a higher value of x, as a positive flux. When the flux is from left to right, the concentration must be higher on the left than on the right, which means that the derivative has a negative value. To obtain a positive value for J one must insert the minus sign as shown.

Were we to take a tank of water, fill it with 42 liters of water, and place a crystal of glucose in one corner, we would find that the movement of glucose through the

tank would be so slow that an animal fed this way would surely die. Diffusion is slow over large distances because the farther one moves from the source, the shallower is the concentration gradient. Within several microns of the source, however, the gradient can be quite large, and over such distances diffusion is an effective means of rapidly distributing material. Distances in the interstitial fluid and within the cells usually are approximately 10 to 20 μm in mammals, and diffusion is the only transport mechanism of significance in these regions. In fact, there is some evidence that cell growth is limited by the speed with which materials can reach the farthest extremes of cells by diffusive mechanisms.

Membrane Transport

Cell membranes are only 40 Å thick. Materials crossing such a membrane must travel a distance that is only a minute fraction of the distance across the interstitial space or through a cell. Despite this major difference in dimensions, transport across cell membranes is usually the slowest process in the distribution of any material throughout the body. We might suspect this by remembering that the concentration of such materials as the strong electrolytes is uniform throughout each compartment but can differ considerably in adjacent compartments separated only by a single thin cell membrane. Thus processes that occur within the cell membranes are primarily responsible for generating these large concentration differences. The mechanisms of membrane transport are varied, involve some of those transport modes already discussed and others as well, and are used by the kidney to regulate body fluids.

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