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Physiology of the Kidney

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PREFACE

The success of the first edition of this text suggested that preparation of a second edition was warranted. In conversations regarding possible alterations and additions, it occurred to us that the scope of the text could be broadened and improved by merging the outlook and experience of a teacher of basic science with those of a teacher of clinical science and practice. If this merger has worked, it is because both of us are primarily renal physiologists with similar interests in research. To that common foundation we have attempted to unite the expertise each of us has acquired from our different training and experience. One of us has taught physiology to first year medical students for more than twenty years. For the last twelve of those years the other has received the same students during their clinical training, has repaired the gaps in their knowledge of physiology and has taught them and house staff how to apply that knowledge to the diagnosis and treatment of disease.

The goal of the text remains the same: to teach the principles of renal physiology to medical students and physicians. We have not attempted to review or survey research in this field; rather we have tried to present a basic statement of the current knowledge of the functions of the kidney, pointing out, where necessary, the imperfections that still exist in that body of knowledge. We hope that our joint effort has enabled this second edition to approach that goal more closely and has made it more relevant to the needs of students and practitioners of medicine.

The changes in this second edition are extensive. We have changed the order in which the various topics are covered. Eight of the thirteen chapters are totally new; only three bear a close resemblance to chapters in the first edition. Two of the chapters cover topics not previously addressed: calcium, magnesium, and phosphate transport and diuretic agents. Two thirds of the figures have been replaced and 38 new figures have been added.

We are immeasurably indebted to the medical students of the Univer-

sity of Kansas School of Medicine for their unwitting but valuable assistance in the preparation of this text. We also wish to acknowledge the assistance of many of our colleagues at this institution. They patiently read and commented on many sections of this text. We particularly wish to thank Drs. Larry Welling and Francis Cuppage who provided the transmission electron micrographs and Dr. Andrew Evan of the University of Indiana who supplied us with the beautiful scanning electron micrographs. We wish to thank Larry Howell and the staff of the Design and Illustration Section at this institution, who beautifully and imaginatively prepared all the new illustrations for this edition. We also wish to thank Linda Carr and Helen Knefel who patiently and accurately typed all the drafts of the manuscript and Lorraine Rome who, despite our reluctance, persuaded us to accept her corrections of punctuation and sentence structure and thereby improved the quality of the final product.

Kansas City, Kansas

Lawrence P. Sullivan

Jared J. Grantham

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CHAPTER 1
Basic Principles

INTRODUCTION

In the process of evolution, the first simple forms of life developed in a fluid medium or environment of a constant composition, the sea. As time progressed, organisms evolved that were able to live first in fresh water and then on dry land. These organisms were able to face a hostile and everchanging external environment because they had developed mechanisms that enabled them to bathe their cells in a constant internal environment. To state it differently, these organisms could live a life relatively free and independent of changes in their external environment because of the constancy of the composition of their internal environment, their extracellular fluids. The attainment of this physiologic freedom was possible to a great extent because of the development of the kidney, the organ primarily responsible for the maintenance of the internal environment.

The kidneys accomplish this vital task in the following way. From the large volume of plasma that the circulation brings to the kidneys daily, the glomeruli filter a fluid almost identical in composition to plasma except for protein. This fluid then flows through the approximately 2,000,000 nephrons in the kidneys. The cells lining these nephrons reabsorb from this fluid specific substances in varying quantities and return them to the blood. These cells also extract additional substances from the blood and secrete them into the urine. As the kidneys perform their task, the process of glomerular filtration and all the myriad tubular mechanisms respond to a variety of factors to return to the circulation a fluid with the composition and volume required to maintain the constancy of the internal environment. In a day's time, the kidneys process the equivalent of the extracellular fluid volume of the body some 15 times by filtering approximately 40 gallons of fluid, reabsorbing from it the necessary amount of various substances and water, and adding

other substances to the urine. Less than half a gallon of fluid with a vastly different composition is finally excreted.

The process of urine formation essentially consists of the transport of water and solute particles through membranes and cell layers. This transport can occur in several ways. In the glomeruli, water and solutes flow together through a porous membrane in response to hydrostatic pressure gradients. In the tubules, water and various types of solute molecules may move across cell layers in different directions at varying rates in response to a variety of forces. Common properties of the membranes and cell layers that substances must cross and basic principles of the mechanisms by which they are transported are reviewed in the following section.

STRUCTURE OF CELL MEMBRANES

Those cell membranes that have been isolated and chemically analyzed consist mainly of protein, cholesterol, and phospholipids. The phospholipids consist of a charged phosphoric end attached to a hydrocarbon chain. The polar end is hydrophilic and the hydrocarbon chain is hydrophobic. Protein molecules are thought to be mainly globular, and may also be bimodal like the phospholipids; that is, one part of the molecule is hydrophilic and the other is hydrophobic.

The lipid molecules within the membrane are arranged in two layers, as indicated in Figure 1-1. The polar hydrophilic ends are in close contact with fluid on each side of the membranes, and the hydrophobic chains are aligned away from water within the interior of the structure. These molecules are not frozen in position; rather, they are believed to move freely in any direction within the plane of the layer. Floating in this lipid layer are globular protein molecules, which may be embedded within only one layer of the lipid molecules or may extend through both layers. The polar or hydrophilic portions of these protein molecules are thought to be in contact with the solutions on either side of the lipid bilayer; the hydrophobic portions are immersed within the lipid bilayer. This construct is considered to be a highly labile, dynamic structure. Some of the protein groups may be free to move in the plane of the membrane and some may appear or disappear with time and in response to various stimuli. Other types of protein may be attached to the membrane in a more peripheral fashion on either surface. Small microfilaments may be attached to the inner surface of the membrane, assisting in holding the membrane in the shape characteristic for the particular cell type. A surface coating of carbohydrate molecules may also be attached to proteins floating in the lipid matrix.

The protein molecules within the membrane and other, extrinsic proteins that may be attached to the surface of the membrane may serve as enzymes catalyzing reactions within and without the cell. They may also serve as receptors for specific chemicals or hormones that affect cell

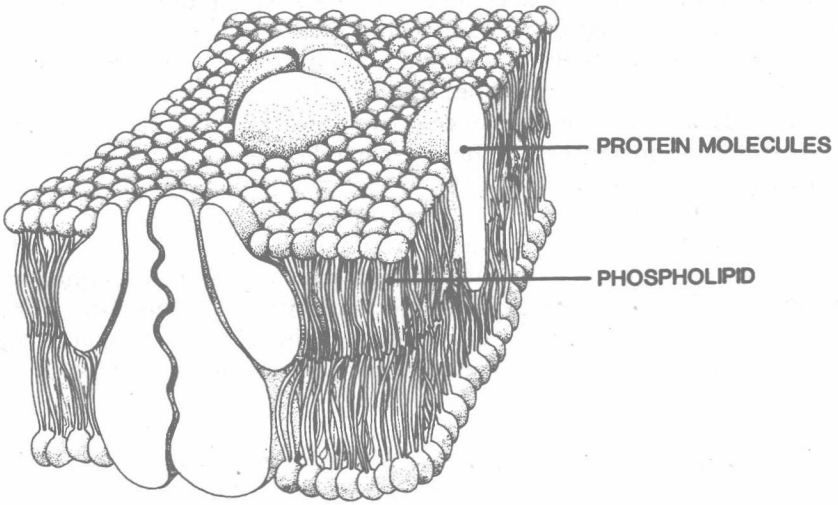

Figure 1-1. A hypothetical view of the structure of the cell membrane. (Adapted from: Singer, S. J.: Architecture and Topography of Biologic Membranes. *In* Weissmann, G., and Clairborne, R., Eds: Cell Membranes. New York, H. P. Publishing Co., 1975; and Sweadner, K. J., and Goldin, S. M.: Active transport of sodium and potassium ions. N. Engl. J. Med. *302*:777, 1980.)

function. The nature of these proteins varies greatly among different cell types.

Molecules may enter or leave the cell through the membrane by a variety of means. Substances such as CO_2, O_2, NH_3, ethanol, and many drugs are soluble in lipid and may easily enter or leave the cell by diffusion through the lipid layer. Here, the limiting factor is not the size of the molecule but its lipid solubility. Substances that are not soluble in lipid, such as water, electrolytes, and many carbohydrates, find the lipid layer an effective barrier to diffusion. However, the protein molecules within the membrane may serve in a variety of ways to permit certain lipid-insoluble substances to cross the membrane. The structure of a protein molecule can be such that a pore or channel through the membrane is formed. The diameter of the channel may limit the size of molecules that can penetrate, but be otherwise unselective, some channels may be lined with positive or negative charges which repel ions of like charge, and others may be much more selective and accept only certain specific molecules.

The presumed diameter of these channels or pores is near the limits of resolution of the electron microscope, so anatomic evidence of their existence is not convincing. These pores may be rigid or dynamic in nature, forming and disappearing with time. Molecular size and con-

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figuration, pore diameter and ionic charge are among the factors limiting penetration by lipid-insoluble compounds through such pores or channels. These channels are thought to occupy only a small fraction of the surface area of a membrane, limiting the rate at which even the smallest lipid-insoluble substances may enter the cells by diffusion. Lipid-soluble substances, on the other hand, have available to them a large fraction of the surface area and can cross the membrane by diffusion at faster rates.

Various cells also possess special mechanisms that transport specific substances across the membrane at rates faster than can be explained by diffusion. In many instances, these mechanisms involve proteins within the membrane that serve as enzymes for chemical reactions that result in the translocation of a specific substance across the membrane.

PASSIVE DIFFUSION

The thermal energy of ions and molecules in a solution causes them to move and collide with one another in a random fashion. In a well-mixed solution, such movement does not change the concentration of the solute or solvent in any one volume unit of the solution, since molecules moving out of such a unit are replaced by molecules moving in. However, if a difference in concentration of a particular molecular species exists between two volume units or between two solutions separated by a membrane, the probability of those molecules moving from the region of high concentration to the region of low concentration exceeds the probability of the molecules moving in the opposite direction. In this situation, a net movement in one direction will take place.

In Figure 1-2 the concentration of substance X is higher in solution A than in B. The probability that molecules of X will move through pores in the membrane from A to B is higher than the probability of their moving in the opposite direction. The net flux of solute particles from A to B equals the difference between the two movements from A to B and from B to A. The magnitude of the net flux (J) of uncharged molecules per unit time is dependent on the magnitude of the concentration difference (ΔC), the permeability per unit surface area of the membrane to the solute (P), and the effective surface area (A) of the membrane available for diffusion of that particular solute. In practice, it is often difficult to determine A and it is more convenient to determine the combination of P and A, the permeability coefficient, k_p.
Thus,

$$J = k_p \Delta C \qquad (1\text{-}1)$$

The k_p of a membrane for a particular solute depends on the temperature; the characteristics of the membrane, such as its thickness, com-

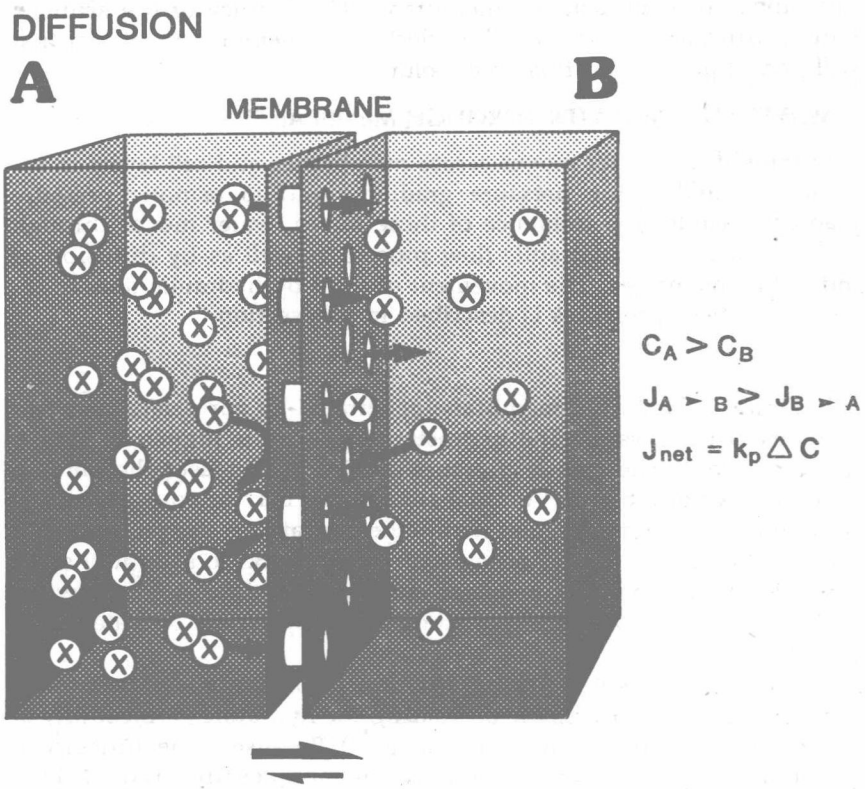

Figure 1-2. Passive diffusion of solute molecules between two solutions separated by a permeable membrane.

position, and surface area; and the characteristics of the diffusing substance, including its size, charge, and lipid solubility.

Diffusion is the primary process by which the exchange of oxygen, carbon dioxide, nutrients, and the products of cell metabolism occurs across cell membranes and capillary membranes in all organs and tissues. It is also the major process by which drugs are absorbed from the gastrointestinal tract into the circulation and by which they reach their site of action from the circulation. Thus, molecular size, charge, and lipid solubility are among the primary determinants of the activity of many drugs. In the clinical procedure of peritoneal dialysis, diffusion is the primary mechanism for exchange of solutes across the peritoneal membrane between the circulation and the dialysate infused into the peritoneal cavity. In hemodialysis of patients with renal failure, solutes are exchanged between the patient's blood and the dialyzing fluid by

diffusion across an artificial membrane. The efficacy of the artificial kidney critically depends on the selection of membrane material that will permit optimum diffusion of solutes.

MOVEMENT OF WATER THROUGH MEMBRANES

In the kidney, water moves across membranes and cell layers in response to hydrostatic pressure gradients and to osmotic pressure gradients. Under the influence of these forces, water moves through pores by a bulk or hydraulic flow process as well as by diffusion of individual molecules. The movement of fluid by hydraulic flow in response to these pressures is described in this section.

Filtration

In Figure 1-3a, a rigid membrane penetrated by pores separates two volumes of pure water. The hydrostatic pressure is higher on side A than on side B. The greater pressure on side A increases the random motion of water molecules on that side, and it may be considered that they bombard water molecules within the pore at a greater rate and with a greater force than do water molecules on side B. To state it another way, the greater activity of water molecules on side A forces water molecules within the pore into side B and a bulk flow of water takes place.

The amount of water filtered per min (J_{H_2O}) is dependent on the pressure difference across the pores (ΔP), the hydraulic permeability of the membrane, (Lp), and its surface area (A). Because of the difficulty of determining Lp and A for many biologic membranes, the product of the two is often determined. This product is called the filtration coefficient (k_f). It is an expression of the permeability of the total membrane to water and has the units of ml per min per mm Hg.
Thus,

$$J_{H_2O} = k_f \Delta P \qquad (1\text{-}2)$$

Osmosis

In Figure 1-3b two volumes of fluid under equal hydrostatic pressure are separated by a membrane permeable only to water. The fluid on side A is pure water, the fluid on side B is a solution of sucrose. Only water exists in the pores within the membrane since sucrose is too large to enter. It has been suggested that this causes a hydrostatic pressure gradient to exist along the length of the pore in the following way. Because of the size of the sucrose molecule, water molecules within the pore are subjected to collision only with water molecules on either side. A larger number of water molecules per unit volume are on side A than on side B, so the number of collisions per unit time between water

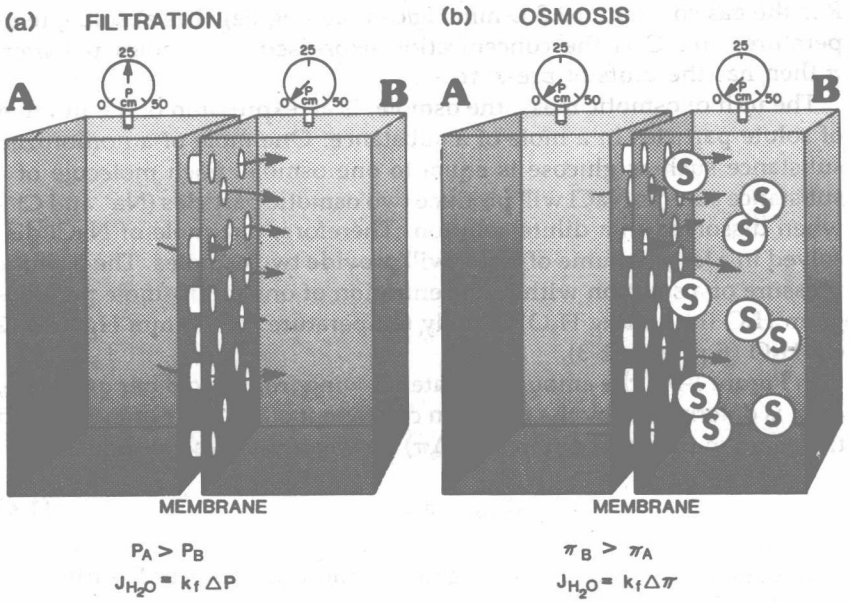

Figure 1-3. (a) Filtration of water through a permeable membrane caused by a hydrostatic pressure gradient. The pressure of each volume of water is indicated by the meter. (b) Osmotic flow of water through a semipermeable membrane caused by an osmotic concentration gradient.

molecules outside the pores and those inside will be greater on side A than on side B, and this will force water molecules within the pores into side B.

A hydrostatic pressure can be applied to side B to stop the flow of water through the pores. Again, it may be considered that this raises the rate of random movement of water molecules (the activity of water) in solution B. The increased number and force of collisions between water molecules on side B and those within the pore become equal to that on side A and thus the net flow of water through the pores becomes zero.

By definition, the osmotic pressure of the solution is that hydrostatic pressure that must be applied to it to stop the net influx of water into the solution from a volume of pure water. Remember that water flows from a region of high water concentration or activity (low solute concentration, low osmotic pressure) to a region of low water concentration or activity (high solute concentration, high osmotic pressure).

The osmotic pressure (π) of a solution is directly related to the concentration of the solute. In an ideal dilute solution

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

R is the gas constant (62.3 L-mm Hg/osmole-degree), T is absolute temperature, and C is the concentration expressed in osmoles per liter. π then has the units of pressure.

The unit of osmotic mass, the osmole, is an expression of the number of solute particles in a mole of a substance. One mole of a nonionized substance such as glucose is equal to one osmole. Each molecule of a substance such as NaCl will produce two osmotic particles (Na^+ and Cl^-) when dissolved in a dilute solution. Therefore, one mole of NaCl dissolved in a large volume of water will provide two osmoles. The osmotic pressure of a solution with a concentration of one milliosmole per kilogram H_2O (mOsm/kg H_2O) at body temperature = 19.3 mm Hg or 26.2 cm H_2O (Equation 1-3).

In Figure 1-3b, the amount of water flowing from A to B per unit time, J_{H_2O}, is determined by the filtration coefficient of the membrane (k_f) and the osmotic pressure difference ($\Delta\pi$) between the two solutions.

$$J_{H_2O} = k_f \Delta\pi \qquad (1\text{-}4)$$

This equation is directly analogous to the one described earlier for filtration (Equation 1-2).

Often the movement of water across a biologic membrane other than a cell membrane results from a combination of osmotic and hydrostatic pressures. Such a situation is illustrated in Figure 1-4a. Two solutions of varying compositions are separated by a rigid, porous membrane. Solution A contains 100 mOsm/kg H_2O of urea and a hydrostatic pressure of 25 cm H_2O is exerted upon it. Solution B has the same concentration of urea, and in addition, contains 2 mOsm/kg H_2O of sucrose. A hydrostatic pressure of 50 cm H_2O is exerted upon it. The membrane has pores with a radius much larger than the radius of the urea molecules but smaller than the radius of sucrose molecules.

Solution A has a total osmotic concentration of 100 mOsm/kg H_2O, that of solution B is 102 mOsm/kg H_2O. However, the membrane will allow urea to move through it with water; thus this solute exerts no effective osmotic pressure. The only effective osmotic pressure results from the presence of sucrose. Therefore, solution A has no effective osmotic concentration ($\pi_A = 0$) and solution B has an effective osmotic concentration (π_B) of 2 mOsm/kg H_2O, or an osmotic pressure of 52.4 cm H_2O at body temperature.

Figure 1-4b illustrates the direction each pressure will tend to cause fluid to flow. The sum of the hydrostatic and osmotic pressures exerted on solution A is greater than that exerted on solution B; the net pressure difference is 27.4 cm H_2O, and that will force fluid to flow from A to B. The flow that results is a bulk flow of solution A. Since the pores are much larger than the urea molecules, urea will pass through the membrane in the stream of water. The concentration of urea in this stream

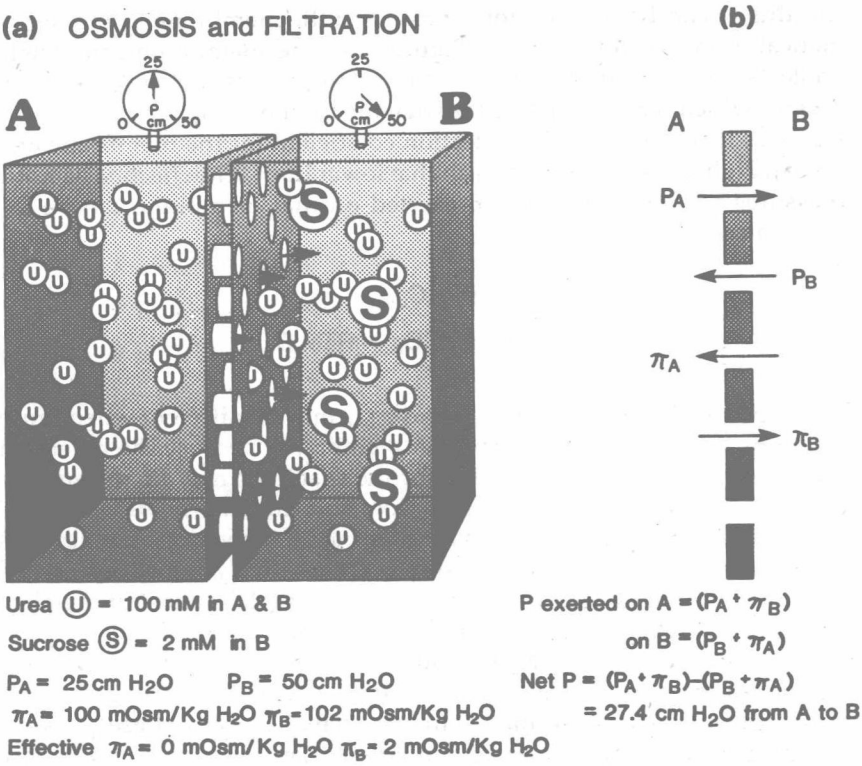

Figure 1-4. (a) Flow of solution through a semipermeable membrane resulting from a combination of hydrostatic and osmotic pressure gradients. (b) The pressures acting to cause flow of fluid through the membrane illustrated in a.

will be the same as in solution A. Therefore, no change in the concentration of urea will take place in either solution A or B as a result of the fluid flow. Such movement of solute particles with the stream of solvent is termed solvent drag.

Reflection Coefficient

The membrane represented in Figure 1-3b was considered to be completely impermeable to the solute. In reality, few combinations of solutes and biologic membranes can be described that way. Most membranes are permeable to some extent to almost all solutes found in body fluids. Because of this, the actual or observed osmotic pressure exerted on a membrane by the presence of a substance in a solution is always somewhat less than that predicted on the basis of its concentration in the solution. The ratio of the two pressures, π_{obs}/π_{theor}, equals σ, the reflection coefficient. The upper limit of the reflection coefficient is 1.0,

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