Mechanism of osmosis

Osmosis is a phenomenon of paramount significance for the transport of water and solutes through biological membranes. It accounts for fluid transport out of the kidney tubules and the gastrointestinal tract, into capillaries, and across cell membranes. The thermodynamic equations for osmosis are well established [1], but, despite the fundamental significance for biological fluid transport, an understanding of osmosis at the molecular level has been lacking.

Osmosis occurs through biological and artificial membranes of widely different composition. The solvent is not necessarily water, but for biological membrane transport, water is the most important solvent. I will restrict the discussion of mechanisms for osmosis to membranes with wide, water-filled channels, which account for osmosis through the capillary and tubular walls, and many other endothelial and epithelial tubes.

Equations for osmotic flow through semipermeable and solute-permeable membranes. The equations for osmotic flow are slightly different through semipermeable and solute-permeable (leaky) membranes. For a semipermeable membrane, the general equation for osmotic flow (J_v) of water is:

$$J_v = L_p (\Delta P - RT\Delta c) \qquad (1)$$

In the equation L_p is a proportionality factor (conductance), ΔP is the hydrostatic pressure difference, and Δc is the difference in osmolal concentration of impermeant solutes between the solutions bathing the membrane; RT is the product of the universal gas constant and the absolute temperature.

For osmotic flow through solute-permeable membranes, as most biological membranes are, a slightly more complicated equation is required. In 1951 Staverman [2] introduced a useful concept, the reflection coefficient (σ) to describe osmosis in solute-permeable membranes. With this coefficient, the equation for osmotic flow through any membrane, semipermeable or solute-permeable, can be written:

$$J_v = L_p (\Delta P - RT\Sigma (\sigma_i \cdot \Delta c_i)) \qquad (2)$$

where $\Sigma (\sigma_i \cdot \Delta c_i)$ is the sum of the products of the reflection coefficient of a substance i and its difference in concentration across the membrane.

A membrane is impermeable to a solute when σ equals 1. If this is true for all solutes bathing the membrane, equation 2 then becomes equation 1. Solutes, with σ equaling zero, flow as readily as water across the osmotic membrane and do not contribute to the osmotic force. It appears from equation 2 that osmotic water transport may well proceed from a solution of high to low total osmolality if an appropriate choice is made of solutes with different reflection coefficients with regard to a particular membrane. Through a semipermeable membrane (equation 1), osmosis always occurs from a high to a low chemical potential for water.

The bombardment hypothesis to explain osmotic pressure. The origin of the kinetic hypothesis stems from calculations made by van't Hoff [3] in 1886 and was based on data obtained by Pfeffer [4]; van't Hoff found that the osmotic pressure of dilute sucrose solutions is proportional to the sucrose concentration and that the proportionality factor is close to RT. These concepts were rapidly extended to dilute electrolyte solutions by taking the extent of ionic dissociation into account [5]. Measurements of osmotic pressure were performed in osmometers equipped with semipermeable membranes which could withstand large hydrostatic pressures. The highest osmotic pressure π was reached when the osmotic flow (J_v) was zero. Hence, van't Hoff's equation $\Delta P = RT\Delta c = \pi$ is a special case of the general equation for osmotic flow.

Van't Hoff [6] suggested a physical explanation in analogy with the kinetic gas theory because of the formal similarity between the equation for osmotic pressure and the ideal gas equation. The basic idea of the kinetic gas theory is that gases are made of elastic molecules which at enormous speeds collide and rebound according to the laws of mechanics. The gas pressure exerted against the walls of the container equals the total momentum transferred by the molecules colliding per unit time.

Van't Hoff's [6] reasoning was that in a solution the water molecules would pass through the osmotic membrane and not influence the osmotic pressure, whereas the impermeant solute molecules would transfer off their momentum to the membrane. He proposed that only the impermeant solute molecules account for the osmotic pressure.

His bombardment hypothesis was received with little enthusiasm by his contemporaries [7] and has in recent years only found few defenders [8, 9]. By definition, impermeant solute molecules must hit the membrane. It is generally accepted that solute molecules behave as gas molecules. What then is wrong with this hypothesis?

The development of a kinetic theory for liquids explaining diffusion. In the course of the 19th century it became clear that the kinetic energy of a molecule is the same in gases and liquids of equal temperature and is the same for solute and solvent molecules of different sizes; the average kinetic energy is 3/2 RT for a gram molecule. Actually, the idea of water and solute molecules behaving as elastic spheres in incessant movement was used to derive the equations for diffusion. Einstein [10] used these ideas and assumed that van't Hoff's law applied to each molecule in a solution. Von Smoluchowski [11] derived the same equations for diffusion without using van't Hoff's law but only by assuming that the water and solute molecules are in incessant zig-zag thermal movement referred to as Brownian motion. A natural extension would have been to connect the phenomenon of osmosis with Brownian motion. However, an attempt by Perrin [12] to explain osmosis in terms of Brownian motion was based on the erroneous assumption that osmotic
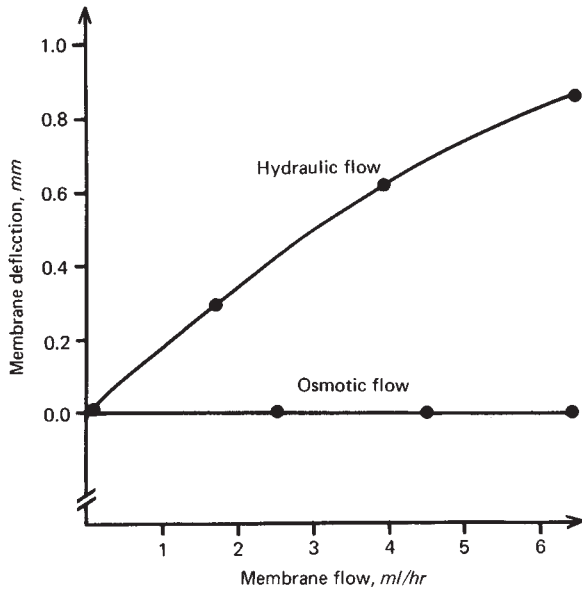
Fig. 1. *Membrane deflection during hydraulic but not during osmotic flow.* Hydraulic flow was induced by progressively raising hydrostatic pressure to 60 mm Hg in the water compartment on one side of a membrane (Amicon UM10) of 50 mm diameter. Osmotic flow was induced by adding polyethylene glycol (mol wt 10,000 daltons) in concentrations up to 12 mM. Membrane deflection was continuously recorded with an ultrasonic technique as the distance between the center of the membrane and the solid chamber wall (unpublished data by S. Leraand and F. Kiil).

Fig. 2. *Left panel:* Brownian motion of water molecules through a membrane pore with water on both sides. No net flow when the hydrostatic pressure is equal on both sides of the membrane ($\Delta P = 0$). *Right panel:* Osmotic flow through a water-filled membrane pore from the water side toward a solution containing impermeant solute molecules in a concentration Δc. Equal hydrostatic pressure on both sides of the membrane. Abbreviations are defined as: J_v, osmotic flow; L_p, conductance; R, gas constant; T, absolute temperature.

pressure is caused by solute bombardment of the membrane. Recently, Villars and Benedek [9] followed similar lines of thought.

The hydrostatic pressure drop in the pore opening. Figure 1 shows that osmotic and hydraulic flows have widely different effects on the membrane.

Osmotic flow between solutions of identical hydrostatic pressure does not deform or deflect even a very thin unsupported membrane, whereas a similar flow induced by a hydrostatic pressure drop across the membrane leads to a bulging or rupture of the membrane. The osmotic pressure is therefore generated by a flow of water through the membrane and development of a hydrostatic pressure on the solution side against the membrane and not by the impact of solute molecules.

Figure 2 illustrates the difference between Brownian motion and osmotic flow. The left panel shows Brownian motion when there are only water molecules on both sides of the membrane. Water molecules in the pore channel move in all directions as indicated by the haphazard direction of the arrows. With equal hydrostatic pressures on both sides of the membrane, an equal number of water molecules will move in and out of the pores, and there will not be any net transport of water. Solute molecules which are so small that they pass unimpaired along the membrane pores would, because of Brownian motion, move from areas of high to areas of low solute concentration, thus accounting for diffusion.

The right panel of Figure 2 illustrates the situation of some water molecules being replaced by solute molecules that are so large they do not enter the pores. The membrane is accordingly
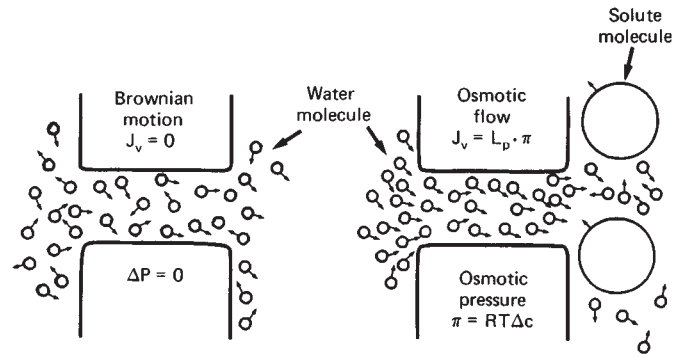
semipermeable with regard to these solute molecules, and in the absence of small solute molecules osmotic flow of water into the solution is generated. As long as the hydrostatic pressure is equal on both sides of the membrane, osmotic flow will continue until the water concentration becomes equal on both sides of the membrane. It is this model of small and large spheres in incessant motion that provides the basis for a kinetic hypothesis.

The first attempt to examine the properties of osmotic flow was made in 1908. Vegard [13] studied osmotic flow at different hydrostatic pressures across an osmotic membrane and drew the conclusion that the hydrostatic pressure drop along the water-filled pores traversing the membrane is the same at equal hydraulic and osmotic flow. This finding has been confirmed repeatedly, and the hydrodynamic conductance L_p is common for the hydraulic and osmotic term in the equations for osmotic flow. However, whereas hydraulic flow requires a difference in hydrostatic pressure across the membrane, osmotic flow proceeds between solutions of identical hydrostatic pressure. In a semipermeable membrane, the change in water concentration occurs at the pore opening on the solution side. It is in the molecular layers in the pore opening that there must be a dramatic change in pressure (Fig. 3). Subsequent researchers [14–16] have tried to provide a physical model for the events taking place in the pore opening. The crucial question is why the hydrostatic pressure in the pore opening is $\Delta P = RT\Delta c$ lower than in the adjacent solution.

The most explicit hypothesis was presented by Dainty [17] who reasoned that the net transport of water out of the pore opening would be the consequence of a difference in water concentration between pore and solution. Dainty wrote that, according to his model, "each molecule oscillates within a confined volume and when owing to the random movement of its neighbor, a hole opens nearby, it will jump into the hole, that is, diffuse and leave a vacancy behind it." Only about 50% of the theoretical pressure drop $RT\Delta c$ can be accounted for by this hypothesis. Moreover, it is not a kinetic hypothesis because it does not visualize the behavior of water molecules as elastic spheres in thermal motion.
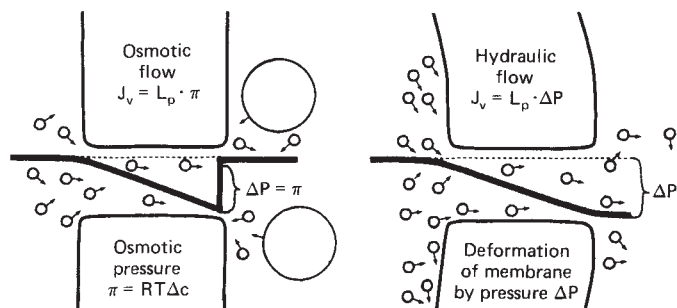
Fig. 3. *Hydrostatic pressure drop along water-filled channels through a membrane during osmotic and hydraulic flow.* Osmotic flow (*left panel*) and hydraulic flow (*right panel*) require the same pressure drop (ΔP) along the membrane pore to generate equal flow (J_v). Hence, the conductance of the pore channels (L_p) is the same during osmotic and hydraulic flow. The osmotic force induced by impermeant solute molecules in concentration Δc is without effect on the membrane at equal hydrostatic pressures on the two sides of the membrane. In contrast, as shown in Figure 1, a hydrostatic pressure difference ΔP during hydraulic flow deforms the membrane (shown in a very exaggerated fashion in the drawing).

Hypothesis compatible with molecular kinetics. Lars Onsager [18] attributed the sudden pressure drop in the pore opening to a momentum deficiency, which is a concept compatible with a kinetic hypothesis. He stated, "There must be a momentum deficiency in the microdomain of the pore on the solution side of the barrier. That is, in a solid region of the barrier, the time average transfer of momentum is that prescribed by the hydrostatic pressure of the phase, but in the opening of the pore there is a deficiency since the momentum arising from the macromolecule is not transferred to the solvent species into the pore."

The pressure on a water-impermeable membrane is not altered by adding solutes on one side. Increased bombardment by solutes against a semipermeable membrane implies reduced bombardment of the pores so that the total pressure is unaltered. Onsager's proposal of a momentum deficiency in the pore opening is therefore a natural extension of van't Hoff's suggestion of a momentum surplus against the solid membrane.

If the water and the solution bathing either side of a semipermeable membrane behaved as ideal gases, the momentum deficiency at the pore opening would account for the pressure drop across the membrane. The number of impacts of solute and water molecules against a pore would be proportional to their molar concentrations. On one side of the membrane is pure water of molar concentration C (55.5 M). On the solution side is the impermeant solute in a concentration Δc. Thus, the first molecular layer of pure water in the pore opening out of reach of the solute molecules would be exposed to a pressure RT (C − Δc) by the water molecules from the solution side and to a pressure RTC by the water molecules in the pore channel. Water molecules would be pushed into the solution by a pressure, π = RTC − RT (C − Δc) = RTΔc, in agreement with expectancy.

The role of intermolecular forces. This simple explanation is not without comments valid for liquids. In contrast to an ideal gas, liquids, and particularly those with water as a solvent, exert large intermolecular forces, which prevent the application of the ideal gas equation to liquids. An interesting possibility is,

however, that intermolecular forces in the water on one side and in the solution on the other side of the membrane are equal and therefore cancel. According to the virial theorem, external and intermolecular forces can be separated.[1] Thus, the pressure pushing water molecules into the solution may be expressed as:

P_1 = RTC + function of intermolecular forces of water.

The pressure in the pore opening from the solution side, counteracting osmotic flow, is expressed as:

P_2 = RT (C − Δc) + function of intermolecular forces of solution.

Thus, if intermolecular forces of water and solution are equal, P_1 − P_2 = RTΔ = π

The reason why van't Hoff's equation does not apply to concentrated solutions is that according to the virial theorem the intermolecular forces on the two sides of the membrane are different. For real gases, attempts have been made to analyze the intermolecular forces in terms of virial coefficients, but there is no way of predicting at which concentration the intermolecular forces of a solution differ significantly from that of water. It is not surprising, however, that the intermolecular forces of water and of a dilute solution of 5 mOsm/kg H_2O do not differ significantly since only one of 10,000 water molecules is replaced by a solute molecule.

The well-established fact that van't Hoff's law does not apply to concentrated solutions provides no argument against the kinetic hypothesis for osmosis. The driving force induced by the momentum deficiency in the pore opening can be counteracted not only by raising the hydrostatic pressure of the solution but also by reducing the hydrostatic pressure of the water on the other side of the supported membrane. Because of the great tensile strength of water (280 atm), negative osmotic pressures of several atmospheres can be attained. In contrast, if a local vacuum was produced in the pore opening, the lowest possible negative pressure would have been one atmosphere.

Kinetic hypothesis explains dependency of osmotic pressure on temperature. The average kinetic energy of both water and solute molecules is proportional to the absolute temperature. The higher the temperature the larger the change in momentum of the molecules hitting the walls of the membrane and the pore openings. The first inaccessible layer of water molecules in the pore opening receives accordingly a greater momentum change as the temperature rises from both sides, but the ratio of the number of impacts is determined by the water concentrations on the two sides of the layer and not by the temperature. Hence, the difference in pressure across the first solid inaccessible layer of water molecules in the pore opening, π, increases in proportion to the absolute temperature.

Influences of the reflection coefficient. For solute-permeable membranes, the reflection coefficient Staverman used [2], which reduces the effective osmotic pressure from π to σ π, is readily incorporated into a kinetic hypothesis for osmosis,

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[1]The virial theorem states that the external pressure of a fluid is:

$$P = CRT + 1/3V \left(\Sigma \, F_{ij} \cdot r_{ij}\right) \text{ average}$$

where C is the molar concentration and V is the molar volume of the fluid. The time average of the sum of scalar products of internal forces F_{ij} and their position vectors r_{ij} must be calculated for all pairs of molecules [19].

Osmotic
pressure: $P_1 - P_2$ =

$\Delta P = \pi = RT\Delta c$

First layer of water
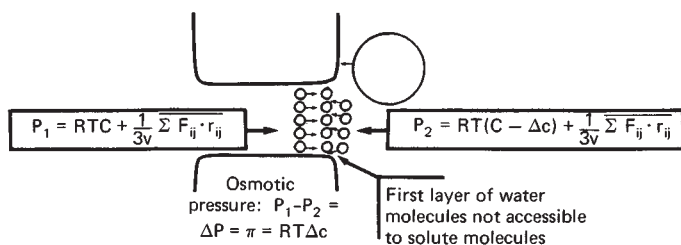molecules not accessible
to solute molecules

Fig. 4. *Kinetics of osmosis and viral theorem.* The membrane is hit by water and solute molecules in proportion to their molar concentrations. The water molecules in the first layer of the pure water in the pore are inaccessible to direct contact with the solute molecules which are reflected by the membrane. Therefore, the first layer of water molecules in the pore opening is hit by fewer water molecules from the solution side than from the pure water in the pore channel, and the momentum change is correspondingly less. The pressure drop in the pore opening is the time average of the momentum deficiency per area. The equations expressing the virial theorem for fluids [19] (see text) indicate that the pressure drop in the pore opening accounts for the osmotic pressure $\pi = RT\Delta c$, provided the intermolecular forces of water and dilute solution do not differ. The momentum deficiency in the pore opening can be balanced by lowering the hydrostatic pressure on the left side of the membrane by π so that osmotic flow is stopped.

Osmotic
pressure

$\pi = RT\Delta c\ (\delta_A - \delta_B)$

Osmotic pressure

$\pi = RT(\Delta C_A \cdot \delta_A - \Delta C_B \cdot \delta_B)$

Fig. 5. *Upper panel: Osmotic flow between solutions of equimolar concentration (isotonic flow).* Although the solute concentrations are equal Δc, osmotic flow proceeds from left to right because the reflection coefficient for solute A, σ_A, is larger than for solute B, σ_B. *Left lower panel: Osmotic flow of permeable solute B from a low to a high concentration.* If solute A was absent there would be no osmotic flow, but there would be a diffusional flow of solute B from left to right. In the presence of solute A there is a net transport of solute B from right to left when the osmotic flow of solute B exceeds the diffusional flow in the opposite direction. This figure illustrates the passive nonenergy-requiring transport of solute B against a concentration gradient. *Right lower panel: Osmotic flow of water and permeant solute from a low to a high water concentration.* Permeant solute behaves like water molecules.

although the molecular events may be difficult to interpret in detail. A large solute molecule has a smaller chance of entering a pore than a water molecule, but even if it enters it may, because of its proximity with the pore walls, reduce flow [20]. The relative size of the solute molecule is only one important factor. Membrane charge, steric hindrance, and solubility in the membrane may influence the reflection coefficient and complicate the interpretation. A permeant solute in concentration c_B and reflection coefficient σ_B is transported into the membrane at a rate of $J_B = c_B(1 - \sigma_B) \cdot J_v$, whether the flow J_v is caused by hydraulic or osmotic pressures. In addition, a permeable solute is transported through the membrane by diffusion along a concentration gradient. For instance, in the proximal tubules a reflection coefficient for sodium chloride of 0.6 has been measured [21]. Thus, osmotic flow through the proximal tubular wall is not only water, but also sodium chloride, although in a lower concentration than in the tubular fluid. This osmotic transport of sodium chloride accounts for the low energy requirements of sodium reabsorption in the proximal tubules [22].

The concept of a reflection coefficient can readily be extended to electrolytes. Because of the attraction forces between anions and cations, the probability of an ion hitting a pore opening is increased if the counter-ion has already hit. Thus, the mutual attraction between counter-ions tends to decrease the reflection coefficient for the whole salt relative to the reflection coefficient for the single ions [24]. Another important rule is that it is the large and less permeant ion which determines the reflection of the whole salt. For this reason, the reflection coefficient in a membrane with water-filled pores would be higher for sodium bicarbonate than for sodium chloride.

Solute transport by osmotic force provided by other solutes. Figure 5 illustrates three simple but important transport situations. The upper level of Figure 5 deals with isosmotic transport. If the solutions on both sides of a membrane have the same osmolal concentration but different composition, osmotic
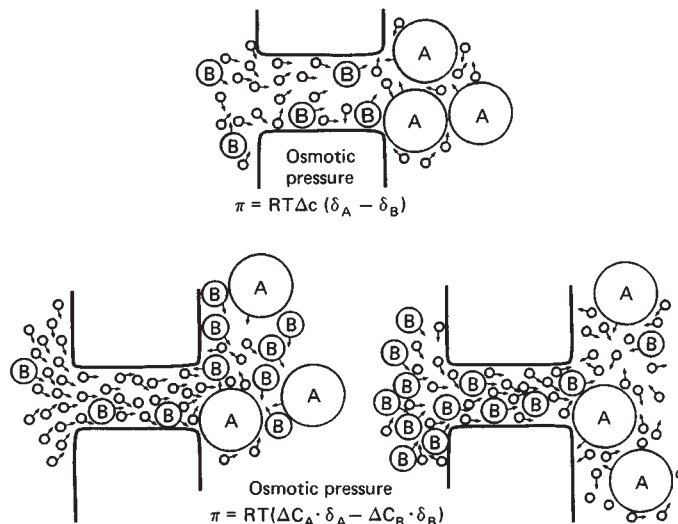
flow takes place provided the sum of the products of solute concentrations and their reflection coefficients is higher on one side of the membrane than on the other. This principle is of significance for the proximal tubular transport of isotonic fluid [23].

The lower left panel of Figure 5 illustrates that the transport of small solute molecules may take place from a low to a high concentration, provided the osmotic flow of solute is greater than the diffusive flow of solute in the opposite direction. Consequently, transport of a solute against a chemical (and electrochemical) gradient is a criterion for active transport only when passive osmotic transport of the solute can be excluded.

The lower right panel of Figure 5 shows that osmotic flow may take place from a low to a high water concentration or chemical potential of water. Of course these examples of transport against chemical gradients do not defy the principles of thermodynamics but illustrate that in a solute-permeable, biological membrane the solvent is not only water molecules but also the permeant solute molecules.

An objection raised against osmotic forces across the pores. Hammel and Scholander [8] have criticized the hypothesis that the lowering of the chemical potential is somehow linked to the impact of solute molecules on the pore openings. Their argument is that only a small fraction of all pore openings would be hit at any time, while the majority of pores would allow back-leakage. For instance, if the pores have a cross-section of 100 water molecules, only one of 100 pores would simultaneously be hit by a solute molecule in a 5 mOsm/kg H_2O solution. To explain osmosis, they advocated a hypothesis based on con-

cepts such as tensile water, which does not provide a physical description of osmosis; their hypothesis has also been criticized for other reasons [25–27].

The objection can be readily met. The kinetic hypothesis readily explains why solute molecules, although present in only one of 100 pores simultaneously, can ensure an osmotic flow which by all measures is continuous. The reason is that pressure in a fluid is not caused by a constant force but is the time average of numerous momentum transfers against an area. The collision frequency of molecules is less well established for liquids than for gases but is for water in the order of at least 10^{11} per sec for each molecule [28]. Large solute molecules are hit even more often because of their larger dimensions. On the other hand, they move much slower than water molecules. During osmotic flow, convection may increase the mixing of solute and water in the liquid layer adjacent to the membrane, but this layer may be unstirred when the osmotic flow approaches zero as the osmotic pressure builds up. However, even the diffusion of large solute molecules is sufficiently rapid to ensure mixing of solute between adjacent molecular layers within fractions of a millisecond.[2] Thus, even a narrow pore in a membrane exposed to a dilute solution would be hit by solute molecules so often that their momentum deficiency would be evenly distributed among all pores in less than a second.

Why solute bombardment does not deform the osmotic membrane. Finally, I want to reemphasize the very important differences between hydraulic and osmotic transport of water and solutes shown in Figure 1: The membrane is deformed by hydraulic forces but not by osmotic forces. The kidney tubules may be exposed to an osmotic force of 250 mOsm/kg H_2O, which corresponds to a hydrostatic transmural pressure of about 5,000 mm Hg. This pressure would disrupt tubular walls. Osmotic forces are therefore much more suitable than hydraulic forces for transport of water through biological membranes because no membrane support is required.

Because the pressure drops along the pore during osmotic flow, there is a frictional force which would move the membrane in the direction of osmotic flow. This force may be counteracted by the excess solute bombardment of the solid membrane. However, the forces involved may be too small to be measurable even when there is a large momentum deficiency in the pore opening. The reason is that the cross-section of the pores is small compared with the area of the solid membrane. Capillaries are much more water-permeable than renal tubules; nevertheless, only 0.002% of the total capillary surface area is available for osmotic flow provided water is transported only across the tight junction between the endothelial cells of capillaries [30]. Because force is the product of pressure and area, the surplus force on the solid membrane is distributed over an area which is 100/0.002 or 50,000 times the area of the

pore openings. The excess pressure against the solid membrane would be 50,000 times lower than the pressure deficit in the pore opening. Even if a tubule were as water permeable as a capillary and exposed to an osmotic concentration of 250 mOsm/kg H_2O corresponding to 5,000 mm Hg, the transmural hydrostatic pressure difference acting on the solid membrane would only be 0.1 mm Hg. It cannot be excluded, however, that water flows through the whole surface of the capillary cells rather than only through the tight junction; in this case the area available for osmotic flow would be 10 to 15 times larger [31]. But even under this condition the transmural pressure difference would not amount to more than 1 to 2 mm Hg and be difficult to measure.

Conclusions

The kinetic hypothesis of osmosis explains why osmotic flow is proportional to the absolute temperature and to the difference in osmolal concentration across the membrane. It explains why permeant solute molecules behave as water molecules, and it accounts for the fact that, in a dilute solution, osmotic flow proceeds although only a few pores are hit by solute molecules simultaneously. It is also consistent with a kinetic hypothesis that the membrane stays stationary during the large osmotic flow between solutions of equal hydrostatic pressure.

A virtue of the kinetic hypothesis is that it explains osmosis at the molecular level without requiring detailed knowledge of the molecular forces acting on the pore opening. Of course, water and solute molecules are not elastic spheres, and this model does not at all explain osmosis through pore-free membranes with solvents other than water. Although restricted to wide, water-filled pores, the kinetics of osmosis provide a useful physical picture of fluid transport through most of the membranes of the body, membranes for dialysis, and numerous other porous membranes.

My interpretation of some mechanisms of proximal tubular function such as isotonic reabsorption and glomerulotubular balance [23, 32] is consistent with a kinetic theory for osmosis and has recently led to a revision of the current view of the mechanism of osmotic diuresis [33]. Despite the explanatory power of the kinetic theory, other theories for osmosis shoud be considered. Until now this important topic has barely been mentioned in treatises on membrane transport. I hope that this presentation will invite constructive dialogue about the mechanisms for osmotic transport.

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[2]In a 5 mM solution, the average distance between adjacent solute molecular layers is X = 6.9 · 10^{-7} cm. For ovalbumin (mol wt, 40,000 daltons), the diffusion coefficient is D = 7.8 · 10^{-7} cm²/sec. According to the Einstein/Smoluchowski equation [29], the time it takes to exchange 50% of the solute molecules between adjacent solute layers is t = X^2/D = 0.06 msec. After hitting a pore, a solute molecule would diffuse back and mix with other solute molecules. Within the next 0.06 msec, a solute molecule would diffuse within a half-sphere containing 270 other solute molecules (P = 0.05), which all may hit the pore in the next 0.06 msec.

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