بسم الله الرحمن الرحيم

Water excretion

WATER EXCRETION

- Normally, 180 L of fluid is filtered through the glomeruli each day, while the average daily urine volume is about 1 L.
- The same ***load of solute*** can be excreted per 24 hours in a urine volume of 500 mL with a concentration of 1400 mosm/kg or in a volume of 23.3 L with a concentration of 30 mosm/kg .
- These figures demonstrate two important facts:
  - first, that at least 87% of the filtered water is reabsorbed, even when the urine volume is 23 L; and
  - second, that the reabsorption of the remainder of the filtered water can be varied **without affecting total solute excretion.**

	GFR (mL/min)	Percentage of Filtered Water Reabsorbed	Urine Volume (L/d)	Urine Concentration (mosm/L)	Gain or Loss of Water in Excess of Solute (L/d)
Urine isotonic to plasma	125	98.7	2.4	290	...
Vasopressin (maximal antidiuresis)	125	99.7	0.5	1400	1.9 gain
No vasopressin ("complete" diabetes insipidus)	125	87.1	23.3	30	20.9 loss

Alterations in water metabolism produced by vasopressin in humans. In each case, the osmotic load excreted is 700 mosm/d.

WATER EXCRETION

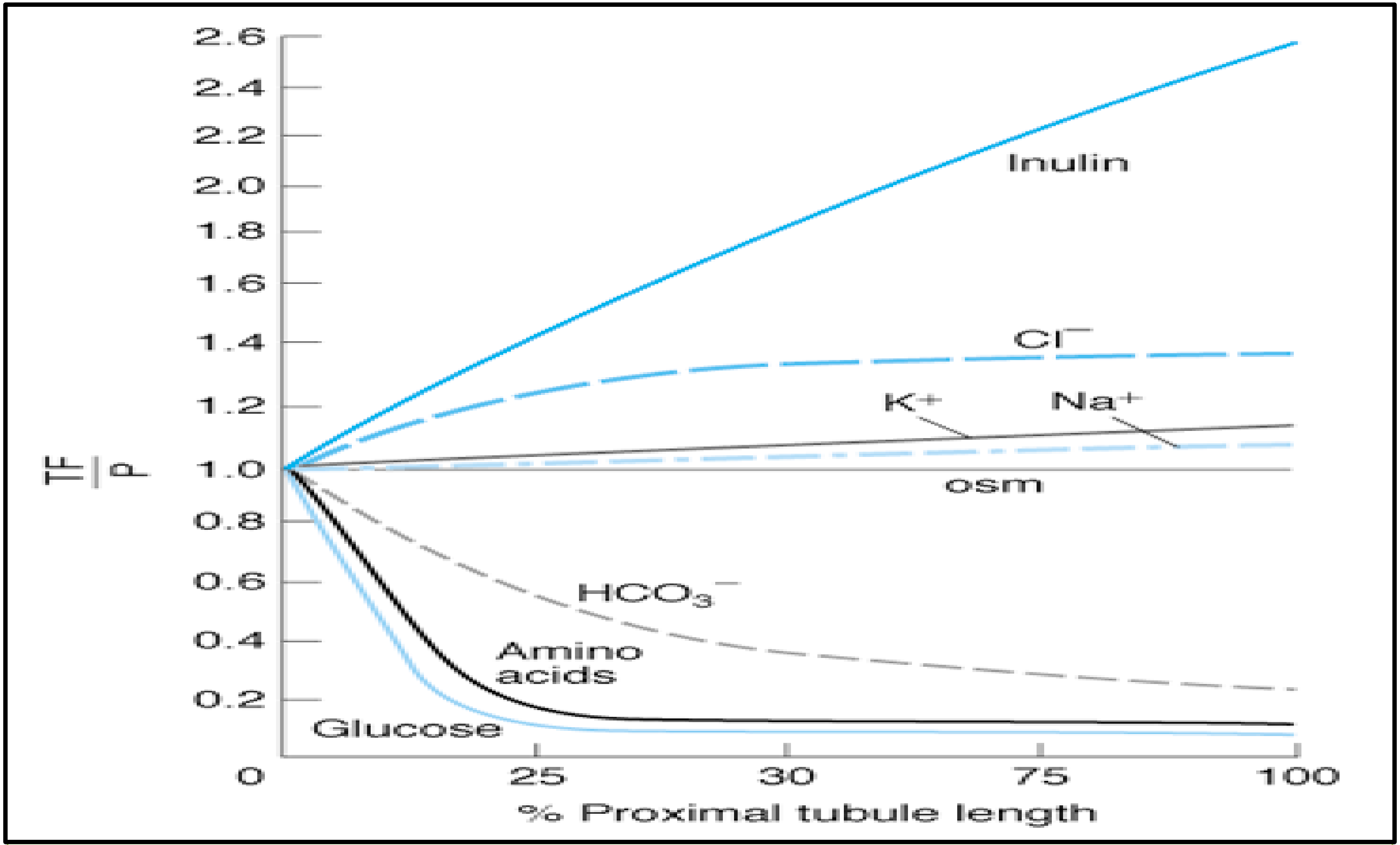
- Therefore, when the urine is ***concentrated***, water is retained in excess of solute; and when it is ***dilute***, water is lost from the body in excess of solute.
- Both facts have great importance in the body economy and the regulation of the osmolality of the body fluids.
- A key regulator of water output is vasopressin acting on the collecting ducts.

Aquaporins

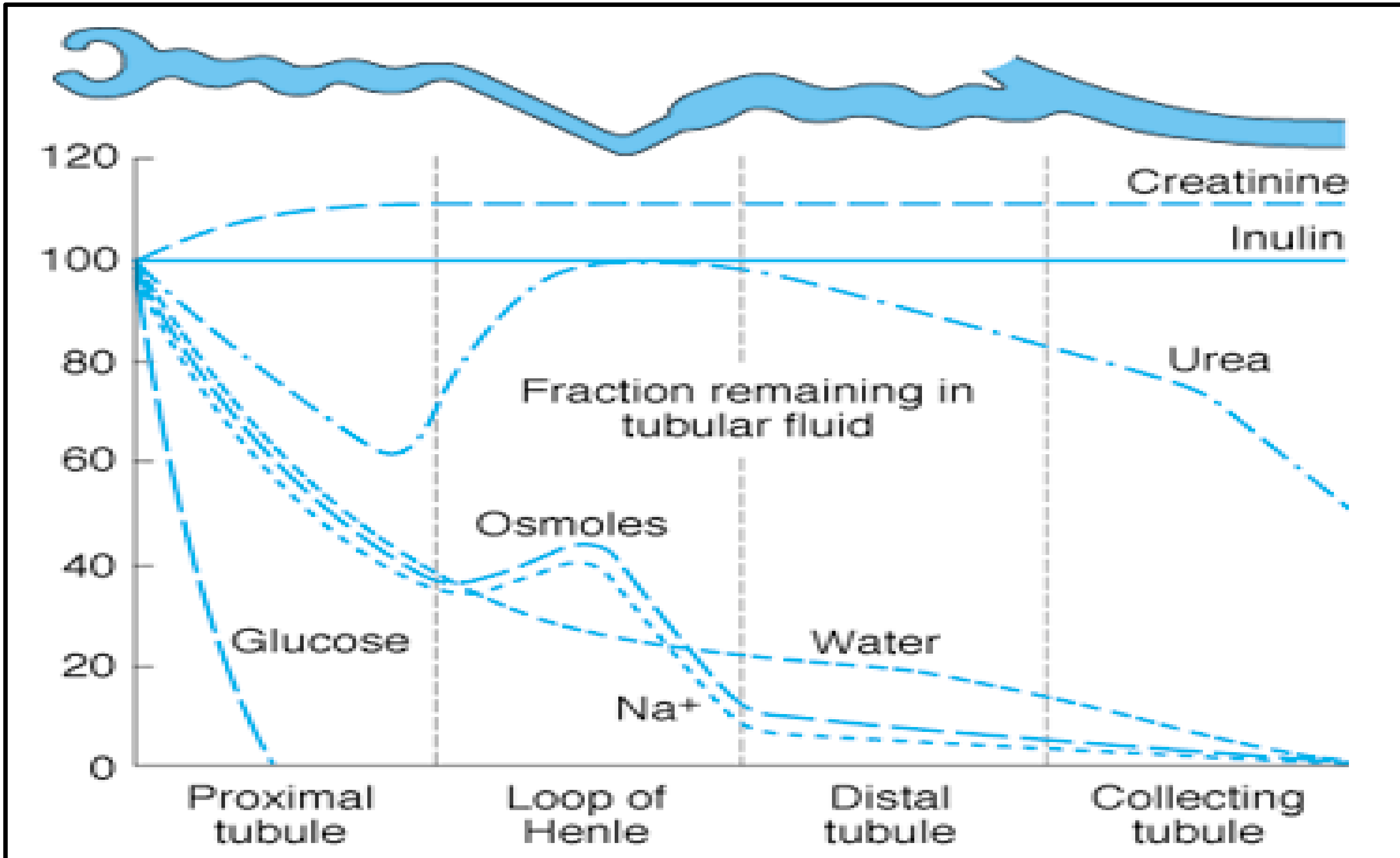
- Research indicates that rapid diffusion of water across cell membranes depends on water channels made up of proteins called **aquaporins**.
- ***Four aquaporins***—aquaporin-1, -2, -5, and -9—have been characterized in humans.
- Most are found in the kidneys, though aquaporin-9 is found in human leukocytes, liver, lung, and spleen; and aquaporin-5 is found in human lacrimal glands.

Proximal Tubule

- Many substances are actively transported out of the fluid in the proximal tubule, but fluid obtained by micropuncture remains essentially isosmotic to the end of the proximal tubule .
- Therefore, in the proximal tubule, water moves passively out of the tubule along the osmotic gradients set up by active transport of solutes, and isotonicity is maintained.
- Since the ratio of the concentration in tubular fluid to the concentration in plasma (TF/P) of the nonreabsorbable substance inulin is 2.5-3.3 at the end of the proximal tubule, it follows that 60-70% of the filtered solute and 60-70% of the filtered water have been removed by the time the filtrate reaches this point .



Reabsorption of various solutes in the proximal tubule. TF/P, tubular fluid:plasma concentration ratio.



Changes in the percentage of the filtered amount of substances remaining in the tubular fluid along the length of the nephron in the presence of vasopressin.

Loop of Henle

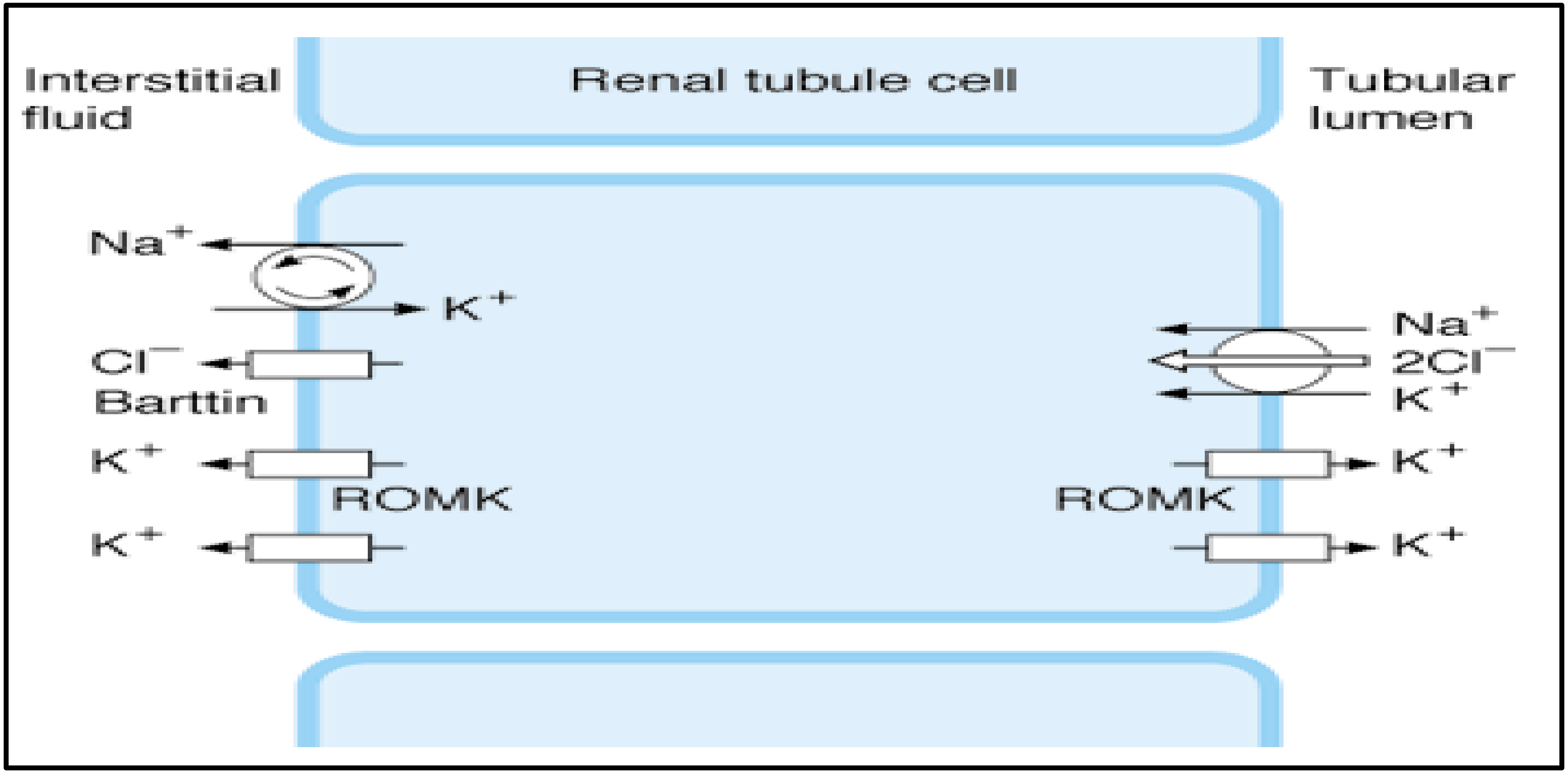
- As noted , the loops of Henle of the juxta-medullary nephrons dip deeply into the medullary pyramids before draining into the distal ***convoluted tubules in the cortex***, and all of the collecting ducts descend back through the medullary pyramids to drain at the tips of the pyramids into the renal pelvis.
- There is a graded increase in the osmolality of the interstitium of the pyramids, the osmolality at the tips of the papillae normally being about 1200 mosm/kg of H_2O, approximately four times that of plasma.
- The descending limb of the loop of Henle is permeable to water, but the ascending limb is impermeable .
- Na^+, K^+, and Cl^- are cotransported out of the thick segment of the ascending limb .

Loop of Henle

- Therefore, the fluid in the descending limb of the loop of Henle becomes hypertonic as water moves into the hypertonic interstitium.
- In the ascending limb it becomes more dilute, and when it reaches the top it is hypotonic to plasma because of the movement of Na^+ and Cl^- out of the tubular lumen.
- In passing through the loop of Henle, another 15% of the filtered water is removed, so approximately 20% of the filtered water enters the distal tubule, and the TF/P of inulin at this point is about 5.

Loop of Henle

- In the thick ascending limb, a carrier cotransports one Na^+, one K^+, and 2 Cl^- from the tubular lumen into the tubular cells.
- This is another example of secondary active transport; the Na^+ is actively transported from the cells into the interstitium by Na^+-K^+ ATPase in the basolateral membranes of the cells, keeping the intracellular Na^+ low.
- The K^+ diffuses back into the tubular lumen and back into the interstitium via ROMK and other K^+ channels.
- The Cl^- diffuses into the interstitium via ClC-Kb channels .
- This K^+ recycles across the luminal and the basolateral membrane, while there is no transport of Na^+ and Cl^- into the interstitium.



NaCl transport in the thick ascending limb of the loop of Henle. The Na^+, K^+, $2Cl^-$ cotransporter moves these ions into the tubular cell by secondary active transport. Na^+ is transported out of the cell into the interstitium by Na^+-K^+ ATPase in the basolateral membrane of the cell. Cl^- exits in basolateral ClC-Kb Cl^- channels. Barttin, a protein in the cell membrane, is essential for normal ClC-Kb function. K^+ moves from the cell to the interstitium and the tubular lumen by ROMK and other K^+ channels.

Distal Tubule

- The distal tubule, particularly its first part, is in effect an extension of the thick segment of the ascending limb.
- It is relatively impermeable to water, and continued removal of the solute in excess of solvent further dilutes the tubular fluid.
- About 5% of the filtered water is removed in this segment.

Collecting Ducts

- The collecting ducts have two portions:
  - a cortical portion and
  - a medullary portion.
- The changes in osmolality and volume in the collecting ducts depend on the amount of vasopressin acting on the ducts.
- This antidiuretic hormone from the posterior pituitary gland increases the permeability of the collecting ducts to water.
- The key to the action of vasopressin on the collecting ducts is aquaporin-2.
- The effect is mediated via the vasopressin V_2 receptor, cyclic AMP, protein kinase A, and a molecular motor, one of the dyneins .

Collecting Ducts

- In the presence of enough vasopressin to produce maximal antidiuresis, water moves out of the hypotonic fluid entering the cortical collecting ducts into the interstitium of the cortex, and the tubular fluid becomes isotonic.
- In this fashion, as much as 10% of the filtered water is removed.
- The isotonic fluid then enters the medullary collecting ducts with a TF/P inulin of about 20.
- An additional 4.7% or more of the filtrate is reabsorbed into the hypertonic interstitium of the medulla, producing a concentrated urine with a TF/P inulin of over 300.
- In humans, the osmolality of urine may reach 1400 mosm/kg of H_2O, almost five times the osmolality of plasma, with a total of 99.7% of the filtered water being reabsorbed

Collecting Ducts

- When vasopressin is absent, the collecting duct epithelium is relatively impermeable to water.
- The fluid therefore remains hypotonic, and large amounts flow into the renal pelvis.
- In humans, the urine osmolality may be as low as 30 mosm/kg of H_2O.
- The impermeability of the distal portions of the nephron is not absolute; along with the salt that is pumped out of the collecting duct fluid, about 2% of the filtered water is reabsorbed in the absence of vasopressin.
- However, as much as 13% of the filtered water may be excreted, and urine flow may reach 15 mL/min or more.

Role of Urea

- Urea contributes to the establishment of the osmotic gradient in the medullary pyramids and to the ability to form a concentrated urine in the collecting ducts.
- Urea transport is mediated by urea transporters, presumably by facilitated diffusion.
- The amount of urea in the medullary interstitium and, consequently, in the urine varies with the amount of urea , and this in turn varies with the dietary intake of protein.
- Therefore, a high-protein diet increases the ability of the kidneys to concentrate the urine.

Water Diuresis

- The **water diuresis** produced by drinking large amounts of hypotonic fluid begins about 15 minutes after ingestion of a water load and reaches its maximum in about 40 minutes.
- The act of drinking produces a small decrease in vasopressin secretion before the water is absorbed, but most of the inhibition is produced by the decrease in plasma osmolality after the water is absorbed.

Water Intoxication

- During excretion of an average osmotic load, the maximal urine flow that can be produced during a water diuresis is about 16 mL/min.
- If water is ingested at a higher rate than this for any length of time, swelling of the cells because of the uptake of water from the hypotonic ECF becomes severe and, rarely, the symptoms of **water intoxication** may develop.
- Swelling of the cells in the brain causes convulsions and coma and leads eventually to death.
- Water intoxication can also occur when water intake is not reduced after administration of exogenous vasopressin or secretion of endogenous vasopressin in response to nonosmotic stimuli such as surgical trauma.

Osmotic Diuresis

- The presence of large quantities of unreabsorbed solutes in the renal tubules causes an increase in urine volume called **osmotic diuresis.**
- Solutes that are not reabsorbed in the proximal tubules exert an appreciable osmotic effect as the volume of tubular fluid decreases and their concentration rises.
- Therefore, they "hold water in the tubules."
- In addition, there is a limit to the concentration gradient against which Na^+ can be pumped out of the proximal tubules.

Osmotic Diuresis

- Normally, the movement of water out of the proximal tubule prevents any appreciable gradient from developing, but Na^+ concentration in the fluid falls when water reabsorption is decreased because of the presence in the tubular fluid of increased amounts of unreabsorbable solutes.

Osmotic Diuresis

- The limiting concentration gradient is reached, and further proximal reabsorption of Na^+ is prevented; more Na^+ remains in the tubule, and water stays with it.
- The result is that the loop of Henle is presented with a greatly increased volume of isotonic fluid.

Osmotic Diuresis

- This fluid has a decreased Na^+ concentration, but the total amount of Na^+ reaching the loop per unit time is increased.
- In the loop, reabsorption of water and Na^+ is decreased because the medullary hypertonicity is decreased.
- The decrease is due primarily to decreased reabsorption of Na^+, K^+, and Cl^- in the ascending limb of the loop because the limiting concentration gradient for Na^+ reabsorption is reached.

Osmotic Diuresis

- More fluid passes through the distal tubule, and because of the decrease in the osmotic gradient along the medullary pyramids, less water is reabsorbed in the collecting ducts.
- The result is a marked increase in urine volume and excretion of Na^+ and other electrolytes.

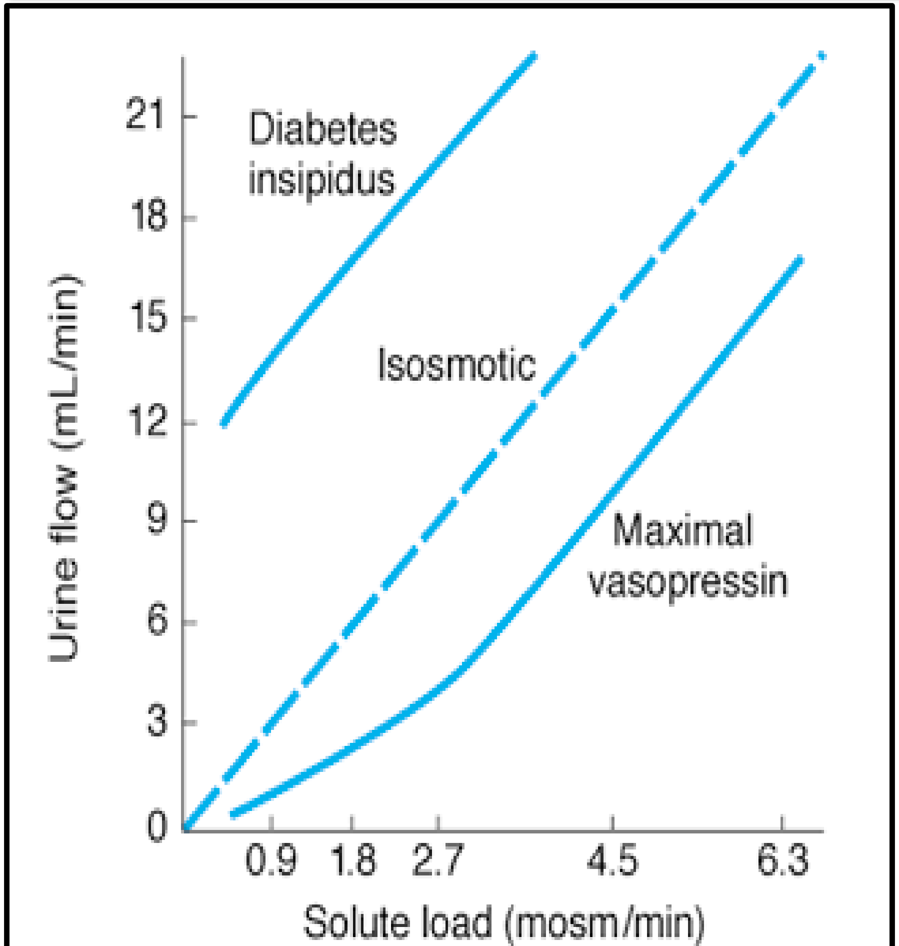
Osmotic Diuresis

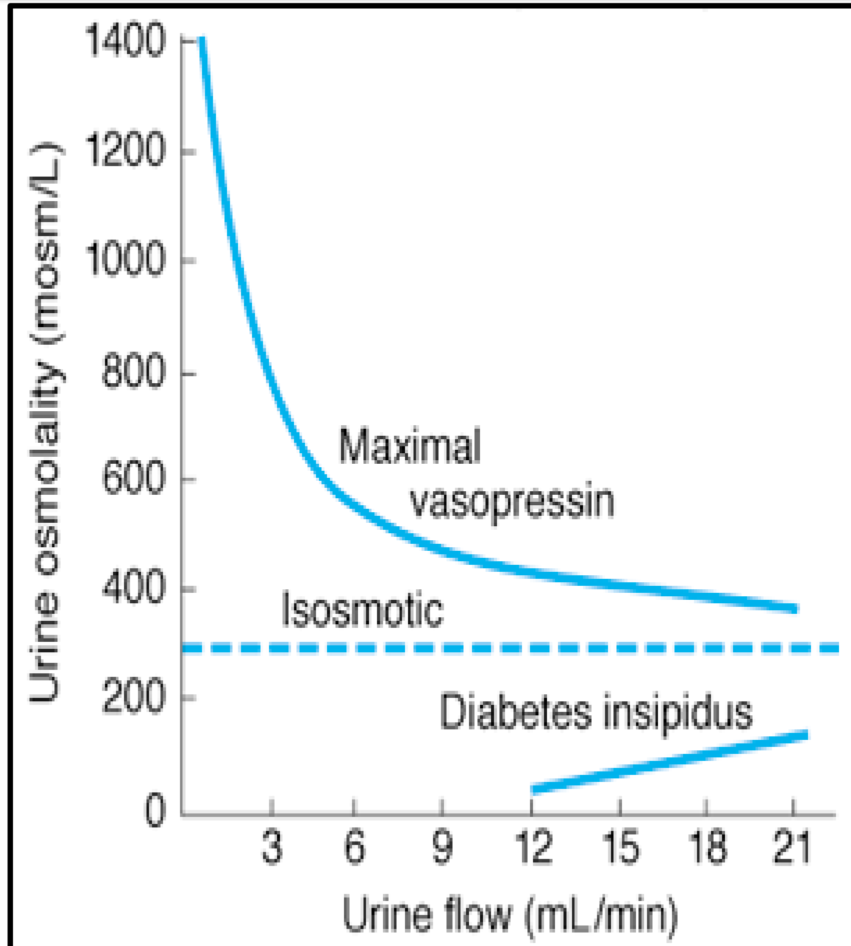
- Osmotic diuresis is produced by the administration of compounds such as mannitol and related polysaccharides that are filtered but not reabsorbed.
- It is also produced by naturally occurring substances when they are present in amounts exceeding the capacity of the tubules to reabsorb them.
- In diabetes mellitus, for example, the glucose that remains in the tubules when the filtered load exceeds the Tm_G causes polyuria.
- Osmotic diuresis can also be produced by the infusion of large amounts of sodium chloride or urea.

Osmotic Diuresis

- It is important to recognize the difference between osmotic diuresis and water diuresis.
- In water diuresis, the amount of water reabsorbed in the proximal portions of the nephron is normal, and the maximal urine flow that can be produced is about 16 mL/min.
- In osmotic diuresis, increased urine flow is due to decreased water reabsorption in the proximal tubules and loops and very large urine flows can be produced.
- As the load of excreted solute is increased, the concentration of the urine approaches that of plasma in spite of maximal vasopressin secretion, because an increasingly large fraction of the excreted urine is isotonic proximal tubular fluid.

Approximate relationship between urine concentration and urine flow in osmotic diuresis in humans. The dashed line in the lower diagram indicates the concentration at which the urine is isosmotic with plasma.





Relation of Urine Concentration to GFR

- The magnitude of the osmotic gradient along the medullary pyramids is increased when the rate of flow of fluid through the loops of Henle is decreased.
- A reduction in GFR such as that caused by dehydration produces a decrease in the volume of fluid presented to the countercurrent mechanism, so that the rate of flow in the loops declines and the urine becomes more concentrated.
- ***When the GFR is low, the urine can become quite concentrated in the absence of vasopressin.***

Thank you