Regulation of Extracellular Fluid Osmolarity and Sodium Concentration

- For the cells of the body to function properly, they must be bathed in extracellular fluid with a relatively constant concentration of electrolytes and other solutes.
- The total concentration of solutes in the extracellular fluid—and therefore the osmolarity—is determined by the amount of solute divided by the volume of the extracellular fluid.
- Extracellular fluid sodium concentration and osmolarity are regulated by the amount of extracellular water.
- The body water in turn is controlled by
  (1) fluid intake, which is regulated by factors that determine thirst
  (2) renal excretion of water, which is controlled by multiple factors that influence glomerular filtration and tubular reabsorption
  (1) the mechanisms that cause the kidneys to eliminate excess water by excreting a dilute urine
  (2) the mechanisms that cause the kidneys to conserve water by excreting concentrated urine.
  (3) the renal feedback mechanisms that control the extracellular fluid sodium concentration and osmolarity.
  (4) the thirst and salt appetite mechanisms that determine the intakes of water and salt,

The Kidneys Excrete Excess Water by Forming a Dilute Urine

The normal kidney has great capability to vary the relative proportions of solutes and water in the urine in response to various challenges.

- When there is excess water in the body and body fluid osmolarity is reduced, the kidney can excrete urine with an osmolarity as low as 50 mOsm/L, a concentration that is only about one sixth the osmolarity of normal extracellular fluid.
- Conversely, when there is a deficit of water and extracellular fluid osmolarity is high, the kidney can excrete urine with a concentration of 1200 to 1400 mOsm/L.
- The kidney can excrete a large volume of dilute urine or a small volume of concentrated urine without major changes in rates of excretion of solutes such as sodium and potassium.
- This ability to regulate water excretion independently of solute excretion is necessary for survival, especially when fluid intake is limited.

- **Antidiuretic Hormone Controls Urine Concentration**

There is a powerful feedback system for regulating plasma osmolarity and sodium concentration that operates by adjusting renal excretion of water independently of the rate of solute excretion.

- A primary effector of this feedback is antidiuretic hormone (ADH), also called vasopressin.
- When osmolarity of the body fluids increases above normal (that is, the solutes in the body fluids become too concentrated), the posterior pituitary gland secretes more ADH, which increases the permeability of the distal tubules and collecting ducts to water.

- ADH action allows enormous amounts of water to be reabsorbed and decreases urine volume but does not significantly change the rate of renal excretion of the solutes.
- When there is excess water in the body and extracellular fluid osmolarity is reduced, the secretion of ADH by the posterior pituitary decreases, thereby reducing the permeability of the distal tubule and collecting ducts to water, which causes enormous amounts of dilute urine to be excreted.
- Thus, the rate of ADH secretion determines largely, whether the kidney excretes a dilute or a concentrated urine.
- **Renal Mechanisms for Excreting a Dilute Urine**
  When there is a large excess of water in the body, the kidney can excrete as much as 20 L/day of dilute urine, with a concentration as low as 50 mOsm/L.
- The kidney performs this by continuing to reabsorb solutes while impeding reabsorption of substantial amounts of water in the distal parts of the nephron, including the late distal tubule and the collecting ducts.
- The approximate renal responses in a human after ingestion of 1 liter of water.
  1-Note that urine volume increases to about six times normal within 45 minutes after the water has been drunk.
- The total amount of solute excreted remains nearly constant because the urine formed becomes very dilute and urine osmolarity decreases from 600 to about 100 mOsm/L.
- After ingestion of excess water, the kidney rids the body of the excess water but does not excrete excess amounts of solutes.
- When the glomerular filtrate is initially formed, its osmolarity is about the same as that of plasma (300 mOsm/L). To excrete excess water, it is necessary to dilute the filtrate as it passes along the tubule.
- This is achieved by reabsorbing solutes to a greater extent than water
- This occurs only in certain segments of the tubular system as follows.
    1. Tubular Fluid Remains Isosmotic in the Proximal Tubule.

  As fluid flows through the proximal tubule, solutes and water are reabsorbed in equal proportions, so that minor change in osmolarity occurs; that is, the proximal tubule fluid remains isosmotic to the plasma, with an osmolarity of about 300 mOsm/L.

    2. As fluid passes down the descending loop of Henle, water is reabsorbed by osmosis and the tubular fluid reaches equilibrium with the surrounding interstitial fluid of the renal medulla, which is very hypertonic—about two to four times the osmolarity of the original filtrate. <u>Therefore, the tubular fluid becomes more concentrated as it flows into the inner medulla.</u>
- **Tubular Fluid Becomes Dilute in the Ascending Loop of Henle.**
  In the ascending limb of the loop of Henle, especially in the thick segment, sodium, potassium, and chloride are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water, even in the presence of substantial amounts of ADH.
- Therefore, the tubular fluid becomes more diluted as it flows up the ascending loop of Henle into the early distal tubule, with the osmolarity decreasing progressively to about 100 mOsm/L by the time the fluid enters the early distal tubular segment.
- Regardless of ADH, fluid leaving the early distal tubular segment is hypo-osmotic, with an osmolarity of only about one third the osmolarity of plasma.

- **Tubular Fluid in Distal and Collecting Tubules Is Further Diluted in the Absence of ADH.** As the dilute fluid in the early distal tubule passes into the late distal convoluted tubule, cortical collecting duct, and collecting duct, there is additional reabsorption of sodium chloride.

- In the absence of ADH, this portion of the tubule is also impermeable to water, and the additional reabsorption of solutes causes the tubular fluid to become even more diluted, decreasing its osmolarity to as low as 50 mOsm/L.

- Absence of water reabsorption along with continued reabsorption of solutes lead to a large volume of dilute urine.
- **In Summary**
- The mechanism for forming a dilute urine is to continue reabsorbing solutes from the distal segments of the tubular system while failing to reabsorb water.
- In healthy kidneys, fluid leaving the ascending loop of Henle and early distal tubule is always diluted, regardless of the level of ADH.
- In the absence of ADH, the urine is further diluted in the late distal tubule and collecting ducts, and a large volume of dilute urine is excreted.

- **The Kidneys Conserve Water by Excreting a Concentrated Urine**

  The ability of the kidney to form a urine that is more concentrated than plasma is essential for survival

Water is continuously lost from the body through various routes, including:

1. the lungs by evaporation into the expired air,
2. the gastrointestinal tract by way of the feces,
3. the skin through evaporation and perspiration,
4. the kidneys through the excretion of urine.

- Fluid intake is required to match this loss, but the ability of the kidney to form a small volume of concentrated urine minimizes the intake of fluid required to maintain homeostasis, a function that is especially important when water supply is limited.
- When there is a water deficit (dehydration)in the body, the kidney forms a concentrated urine by continuing to excrete solutes while increasing water reabsorption and decreasing the volume of urine formed.
- The human kidney can produce a maximal urine concentration of 1200 to 1400 mOsm/L, four to five times the osmolarity of plasma.
- Some desert animals, such as the Australian hopping mouse, can concentrate urine to as high as 10,000 mOsm/L. This allows the mouse to survive in the desert without drinking water;

sufficient water can be obtained through the food ingested and water produced in the body by metabolism of the food.

- In contrary, Animals adapted to aquatic environments, such as the beaver, have minimal urine concentrating ability; they can concentrate the urine to only about 500 mOsm/L.

- **Obligatory Urine Volume**

  The maximal concentrating ability of the kidney dictates how much minimum urine volume must be excreted each day to rid the body of waste products and metabolites and excess ions that are ingested.

- A normal 70-kilogram human must excrete about 600 milliosmoles of solute each day. If maximal urine concentrating ability is 1200 mOsm/L, the minimal volume of urine that must be excreted, called the **obligatory urine volume**, can be calculated as 600/1200= 0.5 L
- 50 msom/L minimal urine conc, then 700/50=12 L max intake

- This minimal loss of volume in the urine contributes to dehydration, along with water loss from the skin, respiratory tract, and gastrointestinal tract, when water is not available to drink.
- The limited ability of the human kidney to concentrate the urine to a maximal concentration of 1200 mOsm/L explains why severe dehydration occurs if you drink seawater.
- Sodium chloride concentration in the ocean averages about 3.0 to 3.5 per cent, with an osmolarity between about 1000 and 1200 mOsm/L.
- Drinking 1 liter of seawater with a concentration of 1200 mOsm/L would provide a total sodium chloride intake of 1200 milliosmoles. If maximal urine concentrating ability is 1200 mOsm/L, the amount of urine volume needed to excrete 1200 milliosmoles would be 1200 milliosmoles divided by 1200 mOsm/L, or 1.0 liter.
- Why then does drinking seawater cause dehydration? The answer is that the kidney must also excrete other solutes, especially urea, which contribute about 600 mOsm/L when the urine is maximally concentrated.
- Thus, for every liter of seawater drunk, more than a liter of urine volume would be required to rid the body of 1200 milliosmoles of sodium chloride ingested in addition to other solutes such as urea. This would result in a net fluid loss
- **Requirements for Excreting a Concentrated Urine**—
  High ADH Levels and Hyperosmotic Renal Medulla
  The basic requirements for forming a concentrated urine are
  (1) an elevated level of ADH, which increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water,
  (2) a high osmolarity of the renal medullary interstitial fluid, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of elevated levels of ADH.
- The renal medullary interstitium surrounding the collecting ducts normally is very hyperosmotic, so that when ADH levels are high, water moves through the tubular membrane by osmosis into the renal interstitium; from there it is carried away by the vasa recta back into the blood.

- We discussed the factors that control ADH secretion later, but for now, what is the process by which renal medullary interstitial fluid becomes hyperosmotic? This process involves the operation of the countercurrent mechanism.

- The countercurrent mechanism depends on the special anatomical arrangement of the loops of Henle and the vasa recta, the specialized peritubular capillaries of the renal medulla.

- In humans, about 25 per cent of the nephrons are juxtamedullary nephrons, with loops of Henle and vasa recta that go deeply into the medulla before returning to the cortex.

- Some of the loops of Henle dip all the way to the tips of the renal papillae that project from the medulla into the renal pelvis.

- Paralleling the long loops of Henle are the vasa recta, which also loop down into the medulla before returning to the renal cortex.

- And finally, the collecting ducts, which carry urine through the hyperosmotic renal medulla before it is excreted, also play a critical role in the countercurrent mechanism.

- **Countercurrent Mechanism Produces a Hyperosmotic Renal Medullary Interstitium**

  The osmolarity of interstitial fluid in almost all parts of the body is about 300 mOsm/L, which is similar to the plasma osmolarity. (As discussed in Chapter 25, the corrected osmolar activity, which accounts for intermolecular attraction and repulsion, is about 282 mOsm/L.)
- The osmolarity of the interstitial fluid in the medulla of the kidney is much higher, increasing progressively to about 1200 to 1400 mOsm/L in the pelvic tip of the medulla.
- This means that the renal medullary interstitium has accumulated solutes in a great excess of water.
- Once the high solute concentration in the medulla is achieved, it is maintained by a balanced inflow and outflow of solutes and water in the medulla.
- The major factors that contribute to the buildup of solute concentration into the renal medulla are as follows:
  1. Active transport of sodium ions and co-transport of potassium, chloride, and other ions out of the thick portion of the ascending limb of the loop of Henle into the medullary interstitium
  2. Active transport of ions from the collecting ducts into the medullary interstitium
  3. Facilitated diffusion of large amounts of urea from the inner medullary collecting ducts into the medullary interstitium
  4. Diffusion of only tiny amounts of water from the medullary tubules into the medullary interstitium, far less than the reabsorption of solutes into the medullary interstitium

  Special Characteristics of Loop of Henle That Cause Solutes to Be Trapped in the Renal Medulla.

The most important cause of the high medullary osmolarity is active transport of sodium and cotransport of potassium, chloride, and other ions from the thick ascending loop of Henle into the interstitium.

- This pump is capable of establishing about a 200- milliosmole concentration gradient between the tubular lumen and the interstitial fluid.
- Because the thick ascending limb is virtually impermeable to water, the solutes pumped out are not followed by osmotic flow of water into the interstitium.
- The active transport of sodium and other ions out of the thick ascending loop adds solutes in excess of water to the renal medullary interstitium.
- There is some passive reabsorption of sodium chloride from the thin ascending limb of Henle's loop, which is also impermeable to water, adding further to the high solute concentration of the renal medullary interstitium.
- The descending limb of Henle's loop, in contrast to the ascending limb, is very permeable to water, and the tubular fluid osmolarity quickly becomes equal to the renal medullary osmolarity. Therefore, water diffuses out of the descending limb of Henle's loop into the interstitium, and the tubular fluid osmolarity gradually rises as it flows toward the tip of the loop of Henle.

- **Steps Involved in Causing Hyperosmotic Renal Medullary Interstitium**.

How does the renal medulla become hyperosmotic?

- First, assume that the loop of Henle is filled with fluid with a concentration of 300 mOsm/L, the same as that leaving the proximal tubule.
- Step 1, the active pump of the thick ascending limb on the loop of Henle is turned on, reducing the concentration inside the tubule, and raising the interstitial concentration; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid.
- Step 2: The limit to the gradient is about 200 mOsm/L because paracellular diffusion of ions back into the tubule eventually counterbalances transport of ions out of the lumen when the 200-mOsm/L concentration gradient is achieved.
- Step 3: is that the tubular fluid in the descending limb of the loop of Henle and the interstitial fluid quickly reach osmotic equilibrium because of osmosis of water out of the descending limb. The interstitial osmolarity is maintained at 400 mOsm/L because of continued transport of ions out of the thick ascending loop of Henle. Thus, by itself, the active transport of sodium chloride out of the thick ascending limb is capable of establishing only a 200-mOsm/L concentration gradient, much less than that achieved by the countercurrent system.
- Step 4 is additional flow of fluid into the loop of Henle from the proximal tubule, which causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb.
- Step 5: Once this fluid is in the ascending limb, additional ions are pumped into the interstitium, with water remaining behind, until a 200-mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity rising to 500 mOsm/L
- Step 6: Then, once again, the fluid in the descending limb reaches equilibrium with the hyperosmotic medullary interstitial fluid, and as the hyperosmotic tubular fluid from the

descending limb of the loop of Henle flows into the ascending limb, still more solute is continuously pumped out of the tubules and deposited into the medullary interstitium.

- Step 7: These steps are repeated over and over, with the net effect of adding more and more solute to the medulla in excess of water; with sufficient time, this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henle, eventually raising the interstitial fluid osmolarity to 1200 to 1400 mOsm/L
- The sodium chloride reabsorbed from the ascending loop of Henle keeps adding to the newly arrived sodium chloride, thus "multiplying" its concentration in the medullary interstitium.
- **Role of Distal Tubule and Collecting Ducts in Excreting a Concentrated Urine**
- When the tubular fluid leaves the loop of Henle and flows into the distal convoluted tubule in the renal cortex, the fluid is diluted, with an osmolarity of only about 100 mOsm/L.
- The early distal tubule further dilutes the tubular fluid because this segment, like the ascending loop of Henle, actively transports sodium chloride out of the tubule but is relatively impermeable to water.
- As fluid flows into the cortical collecting tubule, the amount of water reabsorbed is critically dependent on the plasma concentration of ADH.
- In the absence of ADH, this segment is almost impermeable to water and fails to reabsorb water but continues to reabsorb solutes and further dilutes the urine.
- When there is a high concentration of ADH, the cortical collecting tubule becomes highly permeable to water, so that large amounts of water are now reabsorbed from the tubule into the cortex interstitium, where it is swept away by the rapidly flowing peritubular capillaries.
- The fact that these large amounts of water are reabsorbed into the cortex, rather than into the renal medulla, helps to preserve the high medullary interstitial fluid osmolarity.
- As the tubular fluid flows along the medullary collecting ducts, there is further water reabsorption from the tubular fluid into the interstitium, but the total amount of water is relatively minor compared with that added to the cortex interstitium as the reabsorbed water is quickly carried away by the vasa recta into the venous blood.
- When elevated levels of ADH are present, the collecting ducts become permeable to water, so that the fluid at the end of the collecting ducts has essentially the same osmolarity as the interstitial fluid of the renal medulla—about 1200 mOsm/L.
- Thus, by reabsorbing as much water as possible, the kidneys form a highly concentrated urine, excreting normal amounts of solutes in the urine while adding water back to the extracellular fluid and compensating for deficits of body water.
- Urea contributes about 40 to 50 per cent of the osmolarity (500-600 mOsm/L) of the renal medullary interstitium when the kidney is forming a maximally concentrated urine.
- Unlike sodium chloride, urea is passively reabsorbed from the tubule. When there is water deficit and blood concentrations of ADH are high, copious amounts of urea are passively reabsorbed from the inner medullary collecting ducts into the interstitium.
- The mechanism for reabsorption of urea into the renal medulla is as follows:
  1-As water flows up the ascending loop of Henle and into the distal and cortical collecting tubules, little urea is reabsorbed because these segments are impermeable to urea.

2-In the presence of high concentrations of ADH, water is reabsorbed rapidly from the cortical collecting tubule and the urea concentration increases rapidly because urea is not very permeant in this part of the tubule.
3-When the tubular fluid flows into the inner medullary collecting ducts, more water reabsorption takes place, causing an even higher concentration of urea in the fluid.
4- This high concentration of urea in the tubular fluid of the inner medullary collecting duct causes urea to diffuse out of the tubule into the renal interstitium facilitated by specific urea transporters.

- One of these urea transporters, UT-AI, is activated by ADH, increasing transport of urea out of the inner medullary collecting duct even more when ADH levels are elevated.
  5-The simultaneous movement of water and urea out of the inner medullary collecting ducts maintains a high concentration of urea in the tubular fluid and, eventually, in the urine, even though urea is being reabsorbed.
- The significant role of urea in contributing to urine concentrating ability is shown by the fact that people who ingest a high-protein diet, yielding large amounts of urea as a nitrogenous "waste" product, can concentrate their urine much better than people whose protein intake and urea production are low.
- Malnutrition is associated with a low urea concentration in the medullary interstitium and considerable impairment of urine concentrating ability.

Recirculation of Urea from Collecting Duct to Loop of Henle Contributes to Hyperosmotic Renal Medulla.

A person usually excretes about 20 to 50 per cent of the filtered load of urea.
In general, the rate of urea excretion is determined mainly by two factors:
(1) the concentration of urea in the plasma
(2) the glomerular filtration rate (GFR).
In patients with renal disease who have large reductions of GFR, the plasma urea concentration increases markedly, returning the filtered urea load and urea excretion rate to the normal level (equal to the rate of urea production), despite the reduced GFR.

- With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the papilla, which is about 1200 mOsm/L.
- In the proximal tubule, 40 to 50 per cent of the filtered urea is reabsorbed, but even so, the tubular fluid urea concentration increases because urea is not nearly as permeant as water.
- The concentration of urea continues to rise as the tubular fluid flows into the thin segments of the loop of Henle, partly because of water reabsorption out of the descending loop of Henle but also because of some secretion of urea into the thin loop of Henle from the medullary interstitium.
- The thick limb of the loop of Henle, the distal tubule, and the cortical collecting tubule are all relatively impermeable to urea, and truly little urea reabsorption occurs in these tubular segments.
- When the kidney is forming a concentrated urine and elevated levels of ADH are present, the reabsorption of water from the distal tubule and cortical collecting tubule further raises the tubular fluid concentration of urea.

- And as this urea flows into the inner medullary collecting duct, the high tubular fluid concentration of urea and specific urea transporters cause urea to diffuse into the medullary interstitium.
- A moderate share of the urea that moves into the medullary interstitium eventually diffuses into the thin loop of Henle, so that it passes upward through the ascending loop of Henle, the distal tubule, the cortical collecting tubule, and back down into the medullary collecting duct again.
- In this way, urea can recirculate through these terminal parts of the tubular system several times before it is excreted. Each time around the circuit contributes to a higher concentration of urea.
- **Relevance of recirculation**:
  1-This urea recirculation provides an additional mechanism for forming a hyperosmotic renal medulla.
  2-Because urea is one of the most abundant waste products that must be excreted by the kidneys, this mechanism for concentrating urea before it is excreted is essential to the economy of the body fluid when water is in short supply.

- When there is excess water in the body and low levels of ADH, the inner medullary collecting ducts have a much lower permeability to both water and urea, and more urea is excreted in the urine.
- **Countercurrent Exchange in the Vasa Recta Preserves Hyperosmolarity of the Renal Medulla**
  Blood flow must be provided to the renal medulla to supply the metabolic needs of the cells in this part of the kidney.
- Without a special medullary blood flow system, the solutes pumped into the renal medulla by the countercurrent multiplier system would be rapidly washed out.
- There are two unique features of the renal medullary blood flow that contribute to the preservation of the high solute concentrations:
  1. The medullary blood flow is low, accounting for less than 5 per cent of the total renal blood flow. This sluggish blood flow is sufficient to supply the metabolic needs of the tissues but helps to minimize solute loss from the medullary interstitium.
  2. The vasa recta serve as **countercurrent exchangers**, minimizing washout of solutes from the medullary interstitium.
  The countercurrent exchange mechanism operates as follows
    a. Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla.
    b. The vasa recta, like other capillaries, are highly permeable to solutes in the blood, except for the plasma proteins.
    c. As blood descends into the medulla toward the papillae, it becomes progressively more concentrated, partly by solute entry from the interstitium and partly by loss of water into the interstitium.
    d. By the time the blood reaches the tips of the vasa recta, it has a concentration of about 1200 mOsm/L, the same as that of the medullary interstitium.

e. As blood ascends back toward the cortex, it becomes progressively less concentrated as solutes diffuse back out into the medullary interstitium and as water moves into the vasa recta.
f. Thus, although there is a large amount of fluid and solute exchange across the vasa recta, there is little net dilution of the concentration of the interstitial fluid at each level of the renal medulla because of the U shape of the vasa recta capillaries, which act as countercurrent exchangers.
g. Thus, the vasa recta do not create the medullary hyperosmolarity, but they do prevent it from being dissipated.
h. The U-shaped structure of the vessels minimizes loss of solute from the interstitium but does not prevent the bulk flow of fluid and solutes into the blood through the usual colloid osmotic and hydrostatic pressures that favor reabsorption in these capillaries.
i. Thus, under steady-state conditions, the vasa recta carry away only as much solute and water as is absorbed from the medullary tubules, and the high concentration of solutes established by the countercurrent mechanism is maintained. Increased Medullary Blood Flow Can Reduce Urine Concentrating Ability.
    - Certain vasodilators can markedly increase renal medullary blood flow, thereby "washing out" some of the solutes from the renal medulla and reducing maximum urine concentrating ability.
    - Large increases in arterial pressure can also increase the blood flow of the renal medulla to a greater extent than in other regions of the kidney and tend to wash out the hyperosmotic interstitium, thereby reducing urine concentrating ability.
    - Maximum concentrating ability of the kidney is determined not only by the level of ADH but also by the osmolarity of the renal medulla interstitial fluid. Even with maximal levels of ADH, urine concentrating ability will be reduced if medullary blood flow increases enough to reduce the hyperosmolarity in the renal medulla.

Summary of Urine Concentrating Mechanism and Changes in Osmolarity in Different Segments of the Tubules

Proximal Tubule.

- About 65 per cent of the filtered electrolytes are reabsorbed in the proximal tubule.
- However, the tubular membranes are highly permeable to water, so that whenever solutes are reabsorbed, water also diffuses through the tubular membrane by osmosis.
- Therefore, the osmolarity of the fluid remains about the same as the glomerular filtrate, 300 mOsm/L.

Descending Loop of Henle.

- As fluid flows down the descending loop of Henle, water is absorbed into the medulla. The descending limb is highly permeable to water but much less permeable to sodium chloride and

urea. Therefore, the osmolarity of the fluid flowing through the descending loop gradually increases until it is equal to that of the surrounding interstitial fluid, which is about 1200 mOsm/L when the blood concentration of ADH is high.

- When a dilute urine is being formed, owing to low ADH concentrations, the medullary interstitial osmolarity is less than 1200 mOsm/L; consequently, the descending loop tubular fluid osmolarity also becomes less concentrated.
- This is due partly to the fact that less urea is absorbed into the medullary interstitium from the collecting ducts when ADH levels are low and the kidney is forming a large volume of dilute urine.

Thin Ascending Loop of Henle.

- The thin ascending limb is essentially impermeable to water but reabsorbs some sodium chloride.
- Because of the high concentration of sodium chloride in the tubular fluid, owing to water removal from the descending loop of Henle, there is some passive diffusion of sodium chloride from the thin ascending limb into the medullary interstitium.
- The tubular fluid becomes more dilute as the sodium chloride diffuses out of the tubule and water remains in the tubule.
- Some of the urea absorbed into the medullary interstitium from the collecting ducts also diffuses into the ascending limb, thereby returning the urea to the tubular system and helping to prevent its washout from the renal medulla.
- This urea recycling is an additional mechanism that contributes to the hyperosmotic renal medulla.

Thick Ascending Loop of Henle.

- The thick part of the ascending loop of Henle is also virtually impermeable to water, but enormous amounts of sodium, chloride, potassium, and other ions are actively transported from the tubule into the medullary interstitium.
- Therefore, fluid in the thick ascending limb of the loop of Henle becomes very dilute, falling to a concentration of about 100 mOsm/L.
- Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood.
- In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid and water diffuses back into the vasa recta. Substantial amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries.

Early Distal Tubule.

- The early distal tubule has properties similar to those of the thick ascending loop of Henle, so that further dilution of the tubular fluid occurs as solutes are reabsorbed while water remains in the tubule.

Late Distal Tubule and Cortical Collecting Tubules.

- In the late distal tubule and cortical collecting tubules, the osmolarity of the fluid depends on the level of ADH.
- With elevated levels of ADH, these tubules are highly permeable to water, and significant amounts of water are reabsorbed. Urea, however, is not very permeant in this part of the nephron, resulting in increased urea concentration as water is reabsorbed.

- This makes most of the urea delivered to the distal tubule and collecting tubule to pass into the inner medullary collecting ducts, from which it is finally reabsorbed or excreted in the urine.
- In the absence of ADH, lesser amounts of water are reabsorbed in the late distal tubule and cortical collecting tubule; thus, osmolarity decreases even further because of continued active reabsorption of ions from these segments.

  Inner Medullary Collecting Ducts.

  The concentration of fluid in the inner medullary collecting ducts also depends on
  (1) ADH stimulation
  (2) the osmolarity of the medullary interstitium obtained by the countercurrent mechanism.
- In the presence of large amounts of ADH, these ducts are highly permeable to water, and water diffuses from the tubule into the interstitium until osmotic equilibrium, with the tubular fluid having about reaching the same concentration as the renal medullary interstitium (1200 to 1400 mOsm/L).
- A very concentrated but small volume of urine is produced when ADH levels are high. Because water reabsorption increases urea concentration in the tubular fluid, and because the inner medullary collecting ducts have specific urea transporters that greatly facilitate diffusion, much of the highly concentrated urea in the ducts diffuses out of the tubular lumen into the medullary interstitium.
- absorption of the urea into the renal medulla contributes to the high osmolarity of the medullary interstitium and the high concentrating ability of the kidney.
- **Summary.**
- Although sodium chloride is one of the principal solutes that contributes to the hyperosmolarity of the medullary interstitium, the kidney can, when needed, excrete a highly concentrated urine that contains little sodium chloride.
- The hyperosmolarity of the urine in these circumstances is due to high concentrations of other solutes, especially of waste products such as urea and creatinine.
- One condition in which this occurs is dehydration accompanied by low sodium intake, low sodium intake stimulates formation of the hormone's angiotensin II and aldosterone, which together cause avid sodium reabsorption from the tubules while leaving the urea and other solutes to maintain the highly concentrated urine.
- Large quantities of dilute urine can be excreted without increasing the excretion of sodium accomplished by decreasing ADH secretion, which reduces water reabsorption in the more distal tubular segments without significantly altering sodium reabsorption.
- There is an obligatory urine volume, which is dictated by the maximum concentrating ability of the kidney and the amount of solute that must be excreted. Therefore, if large amounts of solute must be excreted, they must be accompanied by the minimal amount of water necessary to excrete them.
- example, if 1200 milliosmoles of solute must be excreted each day, this requires at least 1 liter of urine if maximal urine concentrating ability is 1200 mOsm/L.

Quantifying Renal Urine Concentration and Dilution "Free Water" and Osmolar Clearances

- The process of concentrating or diluting the urine requires the kidneys to excrete water and solutes somewhat independently.
- When the urine is dilute, water is excreted in excess of solutes. However, when the urine is concentrated, solutes are excreted in excess of water.
- The total clearance of solutes from the blood can be expressed as the osmolar clearance (Cosm); this is the volume of plasma cleared of solutes each minute, in the same way that clearance of a single substance is calculated: where Uosm is the urine osmolarity, V is the urine flow rate, and Posm is the plasma osmolarity.
- For example, if plasma osmolarity is 300 mOsm/L, urine osmolarity is 600 mOsm/L, and urine flow rate is 1 ml/min (0.001 L/ min), the rate of osmolar excretion is 0.6 mOsm/min (600 mOsm/L X 0.001 L/min) and osmolar clearance is 0.6 mOsm/min divided by 300 mOsm/L, or 0.002 L/min (2.0 ml/min).
- This means that 2 milliliters of plasma are being cleared of solute each minute.

Relative Rates at Which Solutes and Water Are Excreted Can Be Assessed Using the Concept of "Free-Water Clearance."

- Free clearance (CH_2O) is calculated as the difference between water excretion (urine flow rate) and osmolar clearance: Thus, the rate of free-water clearance represents the rate at which solute-free water is excreted by the kidneys.
- When free-water clearance is positive, excess water is being excreted by the kidneys.
- when free-water clearance is negative, excess solutes are being removed from the blood by the kidneys and water is being conserved.
- If urine flow rate is 1 ml/min and osmolar clearance is 2 ml/min, free-water clearance would be -1 ml/min. This means that instead of water being cleared from the kidneys in excess of solutes, the kidneys are actually returning water back to the systemic circulation, as occurs during water supply shortage.
- Thus, whenever urine osmolarity is greater than plasma osmolarity, free-water clearance will be negative, indicating water conservation.
- When the kidneys are forming a dilute urine (that is, urine osmolarity is less than plasma osmolarity), free water clearance will be a positive value, denoting that water is being removed from the plasma by the kidneys in excess of solutes.
- Thus, water free of solutes, called "free water," is being lost from the body and the plasma is being concentrated when free-water clearance is positive.
- **Clinical perspective: Disorders of Urinary Concentrating Ability**
- impairment in the ability of the kidneys to concentrate or dilute the urine appropriately can occur with one or more of the following abnormalities:

  1. Inappropriate secretion of ADH. Either too much or too little ADH secretion results in abnormal fluid handling by the kidneys.

  2. Impairment of the countercurrent mechanism. A hyperosmotic medullary interstitium is required for maximal urine concentrating ability. No matter how much ADH is present, maximal urine concentration is limited by the degree of hyperosmolarity of the medullary interstitium.

3.Failure to Produce ADH: “Central” Diabetes Insipidus. An inability to produce or release ADH from the posterior pituitary can be caused by head injuries or infections, or it can be congenital. Because the distal tubular segments cannot reabsorb water in the absence of ADH, this condition, called “central” diabetes insipidus, results in the formation of a large volume of dilute urine, with urine volumes that can exceed 15 L/day. The thirst mechanisms are activated when excessive water is lost from the body; therefore, as long as the person drinks enough water, large decreases in body fluid water do not occur.

The primary abnormality observed clinically in people with this condition is the large volume of dilute urine. However, if water intake is restricted, as can occur in a hospital setting when fluid intake is restricted or the patient is unconscious (for example, because of a head injury), severe dehydration can rapidly occur.

The treatment for central diabetes insipidus is administration of a synthetic analog of ADH, desmopressin, which acts selectively on V2 receptors to increase water permeability in the late distal and collecting tubules.

Desmopressin can be given by injection, as a nasal spray, or orally, and rapidly restores urine output toward normal

4. Inability of the distal tubule, collecting tubule, and collecting ducts to respond to ADH: Inability of the Kidneys to Respond to ADH: “Nephrogenic” Diabetes Insipidus.

- There are circumstances in which normal or elevated levels of ADH are present, but the renal tubular segments cannot respond appropriately. This condition is referred to as “nephrogenic” diabetes insipidus because the abnormality resides in the kidneys.
- This abnormality can be due to either failure of the countercurrent mechanism to form a hyperosmotic renal medullary interstitium or failure of the distal and collecting tubules and collecting ducts to respond to ADH.
- In either case, large volumes of dilute urine are formed, which tends to cause dehydration unless fluid intake is increased by the same amount as urine volume is increased. Many types of renal diseases can impair the concentrating mechanism, especially those that damage the renal medulla.
- Impairment of the function of the loop of Henle, as occurs with diuretics that inhibit electrolyte reabsorption by this segment, can compromise urine concentrating ability. And certain drugs, such as lithium (used to treat manic-depressive disorders) and tetracyclines (used as antibiotics), can impair the ability of the distal nephron segments to respond to ADH.
- Nephrogenic diabetes insipidus can be distinguished from central diabetes insipidus by administration of desmopressin, the synthetic analog of ADH. Lack of a prompt decrease in urine volume and an increase in urine osmolarity within 2 hours after injection of desmopressin is strongly suggestive of nephrogenic diabetes insipidus.
- The treatment for nephrogenic diabetes insipidus is to correct, if possible, the underlying renal disorder. The hypernatremia can also be attenuated by a low-sodium diet and administration of a diuretic that enhances renal sodium excretion, such as a thiazide diuretic.
- **Control of Extracellular Fluid Osmolarity and Sodium Concentration**
  Regulation of extracellular fluid osmolarity and sodium concentration are closely linked because sodium is the most abundant ion in the extracellular compartment.
- Plasma sodium concentration is normally regulated within close limits of 140 to 145 mEq/ L, with an average concentration of about 142 mEq/L.

- Osmolarity averages about 300 mOsm/L (about 282 mOsm/L when corrected for interionic attraction) and seldom changes more than ±2 to 3 per cent.
- **Estimating Plasma Osmolarity from Plasma Sodium Concentration**
  In most clinical laboratories, plasma osmolarity is not routinely measured. However, because sodium and its associated anions account for about 94 per cent of the solute in the extracellular compartment, plasma osmolarity (Posm) can be roughly approximated as Posm = 2.1 X Plasma sodium concentration
- For instance, with a plasma sodium concentration of 142 mEq/L, the plasma osmolarity would be estimated from the formula above to be about 298 mOsm/L.
- In conditions associated with renal disease, the contribution of two other solutes, glucose, and urea, should be included. Such estimates of plasma osmolarity are usually accurate within a few percentage points of those measured directly.
- Normally, sodium ions and associated anions (primarily bicarbonate and chloride) represent about 94 per cent of the extracellular osmoles, with glucose and urea contributing about 3 to 5 per cent of the total osmoles.
- However, because urea easily permeates most cell membranes, it exerts little effective osmotic pressure under steady-state conditions.
- Therefore, the sodium ions in the extracellular fluid and associated anions are the principal determinants of fluid movement across the cell membrane.
- Although multiple mechanisms control the amount of sodium and water excretion by the kidneys, two primary systems are especially involved in regulating the concentration of sodium and osmolarity of extracellular fluid:
  (1) the osmoreceptor-ADH system
  (2) the thirst mechanism. Osmoreceptor-ADH Feedback System
- When osmolarity (plasma sodium concentration) increases above normal because of water deficit, for example, this feedback system operates as follows:
  1. An increase in extracellular fluid osmolarity (which in practical terms means an increase in plasma sodium concentration) causes the special nerve cells called osmoreceptor cells, located in the anterior hypothalamus near the supraoptic nuclei, to shrink.
  2. Shrinkage of the osmoreceptor cells causes them to fire, sending nerve signals to additional nerve cells in the supraoptic nuclei, which then relay these signals down the stalk of the pituitary gland to the posterior pituitary.
  3. These action potentials conducted to the posterior pituitary stimulate the release of ADH, which is stored in secretory granules (or vesicles) in the nerve endings.
  4. ADH enters the blood stream and is transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules, and medullary collecting ducts.
  5. The increased water permeability in the distal nephron segments causes increased water reabsorption and excretion of a small volume of concentrated urine.
- Thus, water is conserved in the body while sodium and other solutes continue to be excreted in the urine.
- This causes dilution of the solutes in the extracellular fluid, thereby correcting the initial excessively concentrated extracellular fluid.
- The opposite sequence of events occurs when the extracellular fluid becomes too dilute (hypo-osmotic). For example, with excess water ingestion and a decrease in extracellular fluid

osmolarity, less ADH is formed, the renal tubules decrease their permeability for water, less water is reabsorbed, and a large volume of dilute urine is formed.

- This as result concentrates the body fluids and returns plasma osmolarity toward normal.
- **ADH Synthesis in Supraoptic and Paraventricular Nuclei of the Hypothalamus and ADH Release from the Posterior Pituitary**
  The hypothalamus contains two types of magnocellular (large) neurons that synthesize ADH in the supraoptic and paraventricular nuclei of the hypothalamus, about five sixths in the supraoptic nuclei and about one sixth in the paraventricular nuclei.
- Both of these nuclei have axonal extensions to the posterior pituitary.
- Once ADH is synthesized, it is transported down the axons of the neurons to their tips, terminating in the posterior pituitary gland.
- When the supraoptic and paraventricular nuclei are stimulated by increased osmolarity or other factors, nerve impulses pass down these nerve endings, changing their membrane permeability and increasing calcium entry.
- ADH stored in the secretory granules (also called vesicles) of the nerve endings is released in response to increased calcium entry.
- The released ADH is then carried away in the capillary blood of the posterior pituitary into the systemic circulation.
- Secretion of ADH in response to an osmotic stimulus is rapid, so that plasma ADH levels can increase severalfold within minutes, thereby providing a rapid means for altering renal excretion of water.
- A second neuronal area important in controlling osmolarity and ADH secretion is located along the anteroventral region of the third ventricle, called the AV3V region.
- At the upper part of this region is a structure called the subfornical organ, and at the inferior part is another structure called the organum vasculosum of the lamina terminalis.
- Between these two organs is the median preoptic nucleus, which has multiple nerve connections with the two organs as well as with the supraoptic nuclei and the blood pressure control centers in the medulla of the brain.
- Lesions of the AV3V region cause multiple deficits in the control of ADH secretion, thirst, sodium appetite, and blood pressure.
- Electrical stimulation of this region or stimulation by angiotensin II can alter ADH secretion, thirst, and sodium appetite.
- In the vicinity of the AV3V region and the supraoptic nuclei are neuronal cells that are excited by small increases in extracellular fluid osmolarity; hence, the term osmoreceptors has been used to describe these neurons.
- These cells send nerve signals to the supraoptic nuclei to control their firing and secretion of ADH. It is also likely that they induce thirst in response to increased extracellular fluid osmolarity.
- Both the subfornical organ and the organum vasculosum of the lamina terminalis have vascular supplies that lack the typical blood-brain barrier that impedes the diffusion of most ions from the blood into the brain tissue which makes it possible for ions and other solutes to cross between the blood and the local interstitial fluid in this region.
- Thus, the osmoreceptors rapidly respond to changes in osmolarity of the extracellular fluid, exerting powerful control over the secretion of ADH and over thirst.

- **Cardiovascular Reflex Stimulation of ADH Release by Decreased Arterial Pressure and/or Decreased Blood Volume**
- ADH release is also controlled by cardiovascular reflexes that respond to decreases in blood pressure and/or blood volume, including
  (1) the arterial baroreceptor reflexes
  (2) the cardiopulmonary reflexes
- These reflex pathways originate in high-pressure regions of the circulation, such as the aortic arch and carotid sinus, and in the low-pressure regions, especially in the cardiac atria.
- Afferent stimuli are carried by the vagus and glossopharyngeal nerves with synapses in the nuclei of the tractus solitarius.
- Projections from these nuclei relay signals to the hypothalamic nuclei that control ADH synthesis and secretion. Thus, in addition to increased osmolarity, two other stimuli increase ADH secretion:
  (1) decreased arterial pressure
  (2) decreased blood volume.
- Whenever blood pressure and blood volume are reduced, such as during hemorrhage, increased ADH secretion causes increased fluid reabsorption by the kidneys, helping to restore blood pressure and blood volume to normal.
- **Quantitative Importance of Cardiovascular Reflexes and Osmolarity in Stimulating ADH Secretion**
- Either a decrease in effective blood volume or an increase in extracellular fluid osmolarity stimulates ADH secretion.
- However, ADH is considerably more sensitive to slight changes in osmolarity than to similar changes in blood volume.
- For example, a change in plasma osmolarity of only 1 per cent is sufficient to increase ADH levels.
- By contrast, after blood loss, plasma ADH levels do not change appreciably until blood volume is reduced by about 10 per cent.
- With further decreases in blood volume, ADH levels rapidly increase.
- Thus, with severe decreases in blood volume, the cardiovascular reflexes play a key role in stimulating ADH secretion.
- However, the usual day-to-day regulation of ADH secretion during simple dehydration is affected mainly by changes in plasma osmolarity.
- Decreased blood volume, however, greatly enhances the ADH response to increased osmolarity.
  Other Stimuli for ADH Secretion
  ADH secretion can also be increased or decreased by other stimuli to the central nervous system as well as by various drugs and hormones.
- For example, nausea is a potent stimulus for Plasma ADH release, which may increase to as much as 100 times normal after vomiting.
- Additionally, drugs such as nicotine and morphine stimulate ADH release, whereas some drugs, such as alcohol, inhibit ADH release. The marked diuresis that occurs after ingestion of alcohol is due in part to inhibition of ADH release.

- **Role of Thirst in Controlling Extracellular Fluid Osmolarity and Sodium Concentration**

- The kidneys minimize fluid loss during water deficits through the osmoreceptor-ADH feedback system.

- Adequate fluid intake, however, is necessary to counterbalance whatever fluid loss does occur through sweating and breathing and through the gastrointestinal tract.

- Fluid intake is regulated by the thirst mechanism, which, together with the osmoreceptor-ADH mechanism, maintains precise control of extracellular fluid osmolarity and sodium concentration.

- Many of the same factors that stimulate ADH secretion also increase thirst, which is defined as the conscious desire for water.

- Central Nervous System Centers for Thirst

  The same area along the anteroventral wall of the third ventricle that promotes ADH release also stimulates thirst.
- Located anterolaterally in the preoptic nucleus is another small area that, when stimulated electrically, causes immediate drinking that continues as long as the stimulation lasts.
- All these areas together are called the thirst center. The neurons of the thirst center respond to injections of hypertonic salt solutions by stimulating drinking behavior.
- These cells almost certainly function as osmoreceptors to activate the thirst mechanism, in the same way that the osmoreceptors stimulate ADH release.
- Increased osmolarity of the cerebrospinal fluid in the third ventricle has essentially the same effect to promote drinking. It is likely that the organum vasculosum of the lamina terminalis, which lies immediately beneath the ventricular surface at the inferior end of the AV3V region, is intimately involved in mediating this response.
- **Stimuli for Thirst**
- One of the most important is increased extracellular fluid osmolarity, which causes intracellular dehydration in the thirst centers, thereby stimulating the sensation of thirst. The value of this response is obvious: it helps to dilute extracellular fluids and returns osmolarity toward normal.
- Decreases in extracellular fluid volume and arterial pressure also stimulate thirst by a pathway that is independent of the one stimulated by increased plasma osmolarity. Thus, blood volume loss by hemorrhage stimulates thirst even though there might be no change in plasma osmolarity.
- Due to neutral input from cardiopulmonary and systemic arterial baroreceptors in the circulation.
- A third important stimulus for thirst is angiotensin II.
  Studies in animals have shown that angiotensin II acts on the subfornical organ and on the organum vasculosum of the lamina terminalis. These regions are outside the blood-brain barrier, and peptides such as angiotensin II diffuse into the tissues.

- Because angiotensin II is also stimulated by factors associated with hypovolemia and low blood pressure, its effect on thirst helps to restore blood volume and blood pressure toward normal, along with the other actions of angiotensin II on the kidneys to decrease fluid excretion.
- Dryness of the mouth and mucous membranes of the esophagus can elicit the sensation of thirst. As a result, a thirsty person may receive relief from thirst almost immediately after drinking water, even though the water has not been absorbed from the gastrointestinal tract and has not yet had an effect on extracellular fluid osmolarity.
- Gastrointestinal and pharyngeal stimuli influence thirst.
  gastrointestinal distention may partially alleviate thirst; for instance, simple inflation of a balloon in the stomach can relieve thirst. However, relief of thirst sensations through gastrointestinal or pharyngeal mechanisms is short-lived; the desire to drink is completely satisfied only when plasma osmolarity and/or blood volume returns to normal.
- The ability of animals and humans to "meter" fluid intake is important because it prevents overhydration. Experimental studies have repeatedly shown that animals drink almost exactly the amount necessary to return plasma osmolarity and volume to normal.
- **Threshold for Osmolar Stimulus of Drinking**
  The kidneys must continually excrete at least some fluid, even in a dehydrated person, to rid the body of excess solutes that are ingested or produced by metabolism.
- Water is also lost by evaporation from the lungs and the gastrointestinal tract and by evaporation and sweating from the skin.
- Therefore, there is always a tendency for dehydration, with resultant increased extracellular fluid sodium concentration and osmolarity.
- When the sodium concentration increases only about 2 mEq/L above normal, the thirst mechanism is activated, causing a desire to drink water, this is called the threshold for drinking
- Thus, even small increases in plasma osmolarity are normally followed by water intake, which restores extracellular fluid osmolarity and volume toward normal.
- Thus, the extracellular fluid osmolarity and sodium concentration are precisely controlled.

Integrated Responses of Osmoreceptor-ADH and Thirst Mechanisms in Controlling Extracellular Fluid Osmolarity and Sodium Concentration

- In a healthy person, the osmoreceptor-ADH and thirst mechanisms work in parallel to precisely regulate extracellular fluid osmolarity and sodium concentration, despite the constant challenges of dehydration.
- Even with additional challenges, such as high salt intake, these feedback systems are able to keep plasma osmolarity reasonably constant.
- An increase in sodium intake to as high as six times normal has only a small effect on plasma sodium concentration as long as the ADH and thirst mechanisms are both functioning normally.
- When either the ADH or the thirst mechanism fails, the other ordinarily can still control extracellular osmolarity and sodium concentration with reasonable effectiveness, as long as there is enough fluid intake to balance the daily obligatory urine volume and water losses caused by respiration, sweating, or gastrointestinal losses.
- If both the ADH and thirst mechanisms fail simultaneously, plasma sodium concentration and osmolarity are very poorly controlled; thus, when sodium intake is increased after blocking the total ADH-thirst system, relatively substantial changes in plasma sodium concentration do occur.

- In the absence of the ADH-thirst mechanisms, no other feedback mechanism is capable of adequately regulating plasma sodium concentration and osmolarity.

Role of Angiotensin II and Aldosterone in Controlling Extracellular Fluid Osmolarity and Sodium Concentration

- Both angiotensin II and aldosterone play a vital role in regulating sodium reabsorption by the renal tubules.
- When sodium intake is low, increased levels of these hormones stimulate sodium reabsorption by the kidneys and, therefore, prevent large sodium losses, even though sodium intake may be reduced to as low as 10 per cent of normal.
- Conversely, with high sodium intake, decreased formation of these hormones permits the kidneys to excrete enormous amounts of sodium.
- Because of the importance of angiotensin II and aldosterone in regulating sodium excretion by the kidneys, some are confused to think that they also play a vital role in regulating extracellular fluid sodium concentration.
- Although these hormones increase the amount of sodium in the extracellular fluid, they also increase the extracellular fluid volume by increasing reabsorption of water along with the sodium.
- Angiotensin II and aldosterone have little effect on sodium concentration, except under extreme conditions. This relative unimportance of aldosterone in regulating extracellular fluid sodium concentration is shown by the experiment of the Effect of substantial changes in sodium intake on extracellular fluid sodium concentration in dogs under normal conditions and after the antidiuretic hormone (ADH) and thirst feedback systems had been blocked.
- We notice that control of extracellular fluid sodium concentration is poor in the absence of these feedback systems.
- Another experiment: When sodium intake increases more than sixfold under two conditions: (1) under normal conditions and (2) after the aldosterone feedback system has been blocked by removing the adrenal glands and infusing the animals with aldosterone at a constant rate so that plasma levels could not change upward or downward. Note that when sodium intake was increased sixfold, plasma concentration changed only about 1 to 2 per cent in either case.
- This indicates that even without a functional aldosterone feedback system, plasma sodium concentration can be well regulated.
- The same type of experiment has been conducted after blocking angiotensin II formation, with the same result.
- There are two primary reasons why changes in angiotensin II and aldosterone do not have a major effect on plasma sodium concentration.

  1-First, angiotensin II and aldosterone increase both sodium and water reabsorption by the renal tubules, leading to increases in extracellular fluid volume and sodium quantity but minor change in sodium concentrations.

  2- Second, as long as the ADH-thirst mechanism is functional, any tendency toward increased plasma sodium concentration is compensated for by increased water intake or increased plasma ADH secretion, which tends to dilute the extracellular fluid back toward normal.

  3-The ADH-thirst system far overrides the angiotensin II and aldosterone systems for regulating sodium concentration under normal conditions.

- Furthermore, even in patients with primary aldosteronism, who have extremely elevated levels of aldosterone, the plasma sodium concentration usually increases only about 3 to 5 mEq/L above normal.
- Under extreme conditions, caused by complete loss of aldosterone secretion because of adrenalectomy or in patients with Addison's disease (severely impaired secretion or total lack of aldosterone), there is tremendous loss of sodium by the kidneys, which can lead to reductions in plasma sodium concentration. One of the reasons for this is that large losses of sodium eventually cause severe volume depletion and decreased blood pressure, which can activate the thirst mechanism through the cardiovascular reflexes.
- This leads to a further dilution of the plasma sodium concentration, even though the increased water intake helps to minimize the decrease in body fluid volumes under these conditions. Thus, there are extreme situations in which plasma sodium concentration may change significantly, even with a functional ADH-thirst mechanism (ADH is inhibited with low plasma Na).
- The ADH-thirst mechanism is by far the most powerful feedback system in the body for controlling extracellular fluid osmolarity and sodium concentration.
- **Salt-Appetite Mechanism for Controlling Extracellular Fluid Sodium Concentration and Volume** Maintenance of normal extracellular fluid volume and sodium concentration requires a balance between sodium excretion and sodium intake.
- In modern civilizations, sodium intake is almost always greater than necessary for homeostasis. In fact, the average sodium intake for individuals in industrialized cultures eating processed foods usually ranges between 100 and 200 mEq/day, even though humans can survive and function normally on 10 to 20 mEq/day.
- Thus, most people eat far more sodium than is necessary for homeostasis, and there is evidence that our usual high sodium intake may contribute to cardiovascular disorders such as hypertension.
- Salt appetite is due in part to the fact that animals and humans like salt and eat it regardless of whether they are salt-deficient.
- There is also a regulatory component to salt appetite in which there is a behavioral drive to obtain salt when there is sodium deficiency in the body. This is particularly important in herbivores, which naturally eat a low-sodium diet, but salt craving may also be important in humans who have extreme deficiency of sodium, such as occurs in Addison's disease.
- In this instance, there is deficiency of aldosterone secretion, which causes excessive loss of sodium in the urine and leads to decreased extracellular fluid volume and decreased sodium concentration; both of these changes stimulate the desire for salt.
- In general, the two primary stimuli that are believed to increase salt appetite are
  (1) decreased extracellular fluid sodium concentration
  (2) decreased blood volume or blood pressure, associated with circulatory insufficiency.
- The neuronal mechanism for salt appetite is analogous to that of the thirst mechanism.
- Some of the same neuronal centers in the AV3V region of the brain seem to be involved, because lesions in this region frequently affect both thirst and salt appetite simultaneously in animals.
- Also, circulatory reflexes elicited by low blood pressure or decreased blood volume
- **Reference:**
- **Guyton and Hall Text Book of Medical Physiology, first Jordanian edition**