Renal system

PHYSIOLOGY

Very important

Extra information

References :

- GUYTON AND HALL 12th edition
- LINDA 5th edition

* Guyton corners, anything that is colored with grey is EXTRA explanation

Urine Concentration Mechanism

Objectives :

- Identify and describe that the loop of Henle is referred to as countercurrent multiplier and the loop and vasa recta as countercurrent exchange systems in concentrating and diluting urine.
- Explain what happens to osmolarity of tubular fluid in the various segments of the loop of Henle when concentrated urine is being produced.
- Explain the factors that determine the ability of loop of Henle to make a concentrated medullary gradient
- Differentiate between water diuresis and osmotic diuresis
- Appreciate clinical correlates of diabetes mellitus and diabetes insipidus

{ ملاحظة : هذه المحاضرة مبنية بشكل أساسي على شرح قايتون نظراً لكون السلايدات غير كافية للفهم. }

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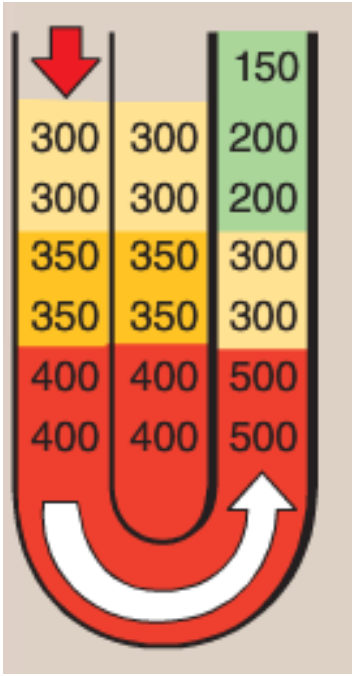
Countercurrent System

Countercurrent System:



- A system in which inflow runs parallel and in close proximity but opposite to the outflow.
- The operation of such a system allows the outgoing fluid to heat the incoming fluid.
- The primary function of loop of henle reabsorbs another 20% of the salt/water in tubular fluid that's which determine osmolarity of urine *(whether concentrated or diluted) using :*
  Countercutrrent multiplier system.
- While collecting duct is where *urine concentration is determined*, Osmolarity of interstitial fluid in **medulla** must be *high* and osmolarity of **tubular fluid** must be *low*.

- **Guyton corner :**

When there is a water deficit in the body, the kidney forms 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.

Before starting the lecture, we recommend you to watch this video.

YouTube

Countercurrent System

Countercurrent multiplier system:

- Is the **repetitive reabsorption of NaCl** by the *thick ascending loop of Henle* and continued inflow of new NaCl from PCT into loop of Henle.

- The NaCl reabsorbed from the ascending Loop of henle **keeps adding newly arrived NaCl** (into LOH from PCT), *thus multiplying its concentration in the medulla.*

- counter current multiplier system is the most important system of LOH, it detect the conc. of urine by salt/water reabsorption.
- why is it called multiplier? Because we keep adding more and more of NaCl to medulla, so it's concentration will increase.

• Guyton corner :

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. The osmolarity of the interstitial fluid in the medulla of the kidney is much higher and may increase 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 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: 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,Active transport of ions from the collecting ducts into the medullary interstitium , Facilitated diffusion of urea from the inner medullary collecting ducts into the medullary interstitium,Diffusion of only small amounts of water from the medullary tubules into the medullary interstitium, far less than the reabsorption of solutes into the medullary interstitium

EXTRA

• Guyton corner :

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

The transport characteristics of the loops of Henle are summarized in Table 28-1, along with the properties of the proximal tubules, distal tubules, cortical collecting tubules, and inner medullary collecting ducts.

		Permeability		
	Active NaCl Transport	H_2O	NaCl	Urea
Proximal tubule	++	++	+	+
Thin descending limb	0	++	+	+
Thin ascending limb	0	0	+	+
Thick ascending limb	++	0	0	0
Distal tubule	+	+ADH	0	0
Cortical collecting tubule	+	+ADH	0	0
Inner medullary collecting duct	+	+ADH	0	++ADH

Table 28-1

• Guyton corner : *[IMPORTANT]*

The most important cause of the high medullary osmolarity is active transport of sodium and co-transport 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. Thus, 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.

EXTRA

For better understanding , read this explanation before studying the next slides

- **Guyton corner :** *[IMPORTANT]*

Steps Involved in Causing Hyperosmotic Renal Medullary Interstitium.

Keeping in mind these characteristics of the loop of Henle, let us now discuss how the renal medulla becomes 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 (Figure 28-4, **step 1**). Next, the active ion pump of the *thick ascending limb* on the loop of Henle reduces the concentration inside the tubule and raises 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. Once this fluid is in the ascending limb, additional ions are pumped into the interstitium, with water remaining in the tubular fluid, until a 200-mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity rising to 500 mOsm/L (**step 5**). Then, once again, the fluid in the descending limb reaches equilibrium with the hyperosmotic medullary interstitial fluid (**step 6**), 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. 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 as shown in **step 7***.Thus, the repetitive reabsorption of sodium chloride by the thick ascending loop of Henle and continued inflow of new sodium chloride from the proximal tubule into the loop of Henle is called the *countercurrent multiplier*. 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

“Steps → next slide”

Steps

link them with the previous explanation

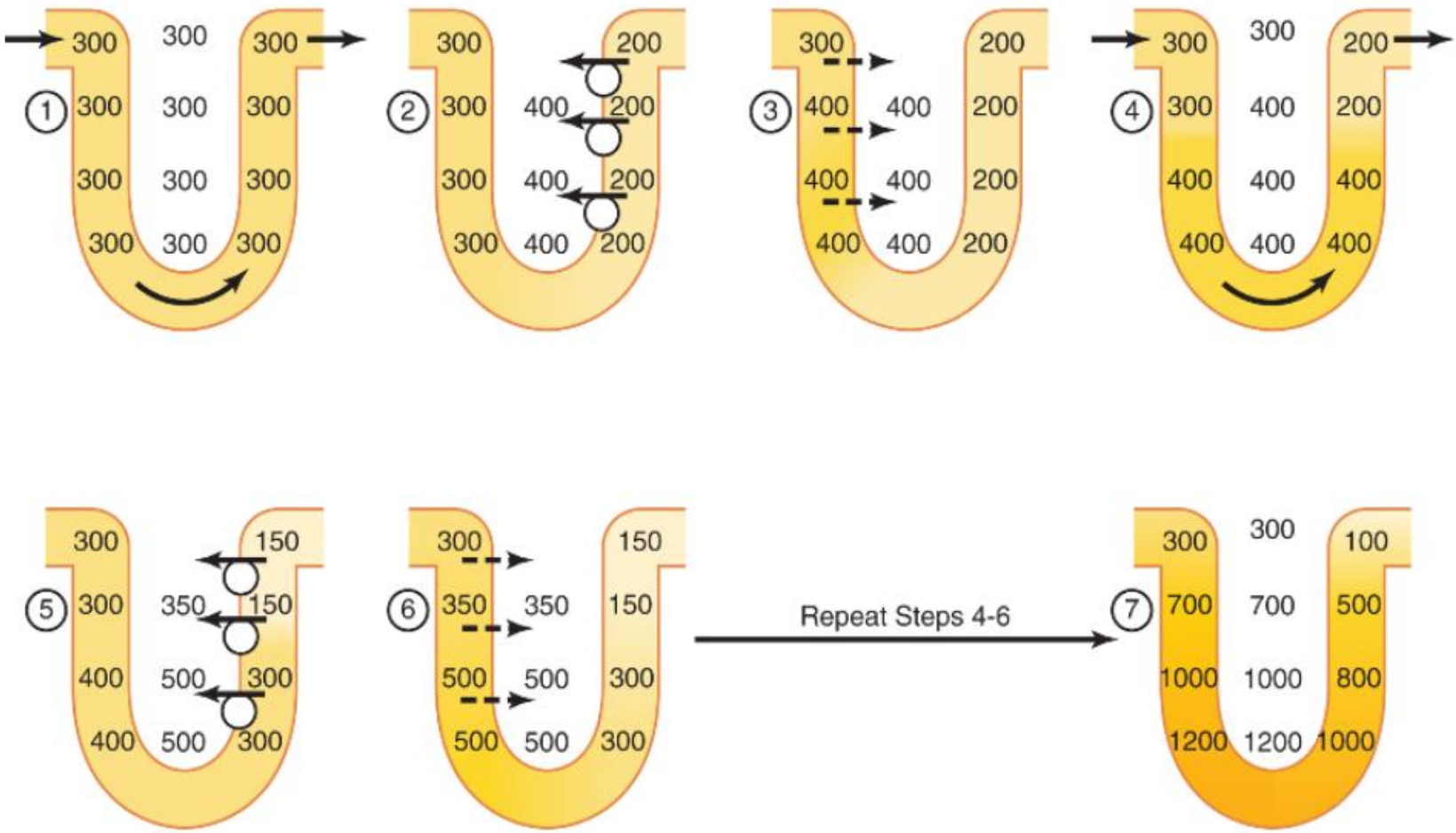


Figure 28-4

Diluted Urine

- Have to be:
  - *low or no ADH*
  - *Reabsorb solute not water*

Isosmotic fluid from Proximal convoluted tubule

↓

Thin descending limb *permeable to water* , less for NaCl

↓

Thin AL *impermeable to water, permeable to NaCl* **(passive)**.
Volume unchanged , ↓ NaCl

↓

Thick AL *impermeable to water*. NaCl reabsorbed **(Active)**
diluting tubule fluid *150 mOsm/kg* water.

TAL = diluting segment of nephron

↓

Collecting duct reabsorb NaCl.
↓ osmolality which reach *50 mOsm/kg* water

- Fluid coming from PCT is isosmotic due to the permeability of Na = water. It won't affect osmolarity. It enter LOH as Isosmotic.
- In the thin descending limb, which is permeable to water, it start reabsorbing water to be equal to medulla conc.
- Now the solutes reach the thin ascending limb which is permeable to Nacl .
- After that they reach the Thick ascending limb which is impermeable to water and permeable to Nacl, the filtrate will be diluted
- لأننا نسحب منه الصوديوم > it will be hyposmotic.
- Collecting duct will reabsorb Nacl , decreasing the osmolarity more and more *(very hyposmotic = 50 !)*

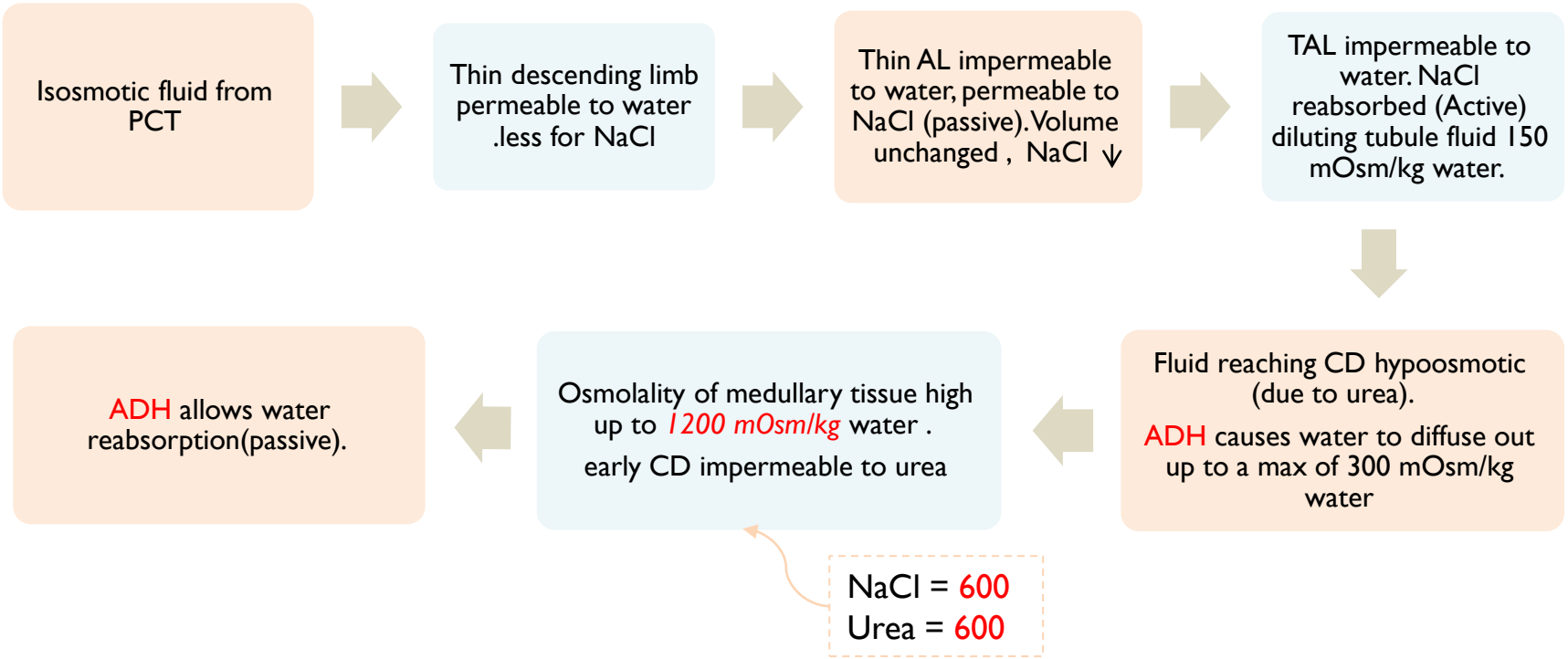
EXTRA

Summary of the previous slide

Urinary Dilution Mechanism					
Structure	**Proximal convoluted tubule**	**Loop of henle**			**Collecting Duct**
		Thin Descending limb	**Thin Ascending limb**	**Thick Ascending limb**	
Permeable to	Both water & NaCl	Only to water	NaCl		Controlled by ADH *(For the urine to be diluted, there is low or no ADH)*
Impermeable to	-	Nacl	Water		
Water reabsorption %	65%	20-25%	ZERO		
Reabsorption	H_2O &NaCl	Water (osmosis)	NaCl (passive)	NaCl (Active)	NaCl
Osmolarity	Isosmotic (300 mOsm/L)	Hyperosmotic	Hyposmotic		Hyposmotic

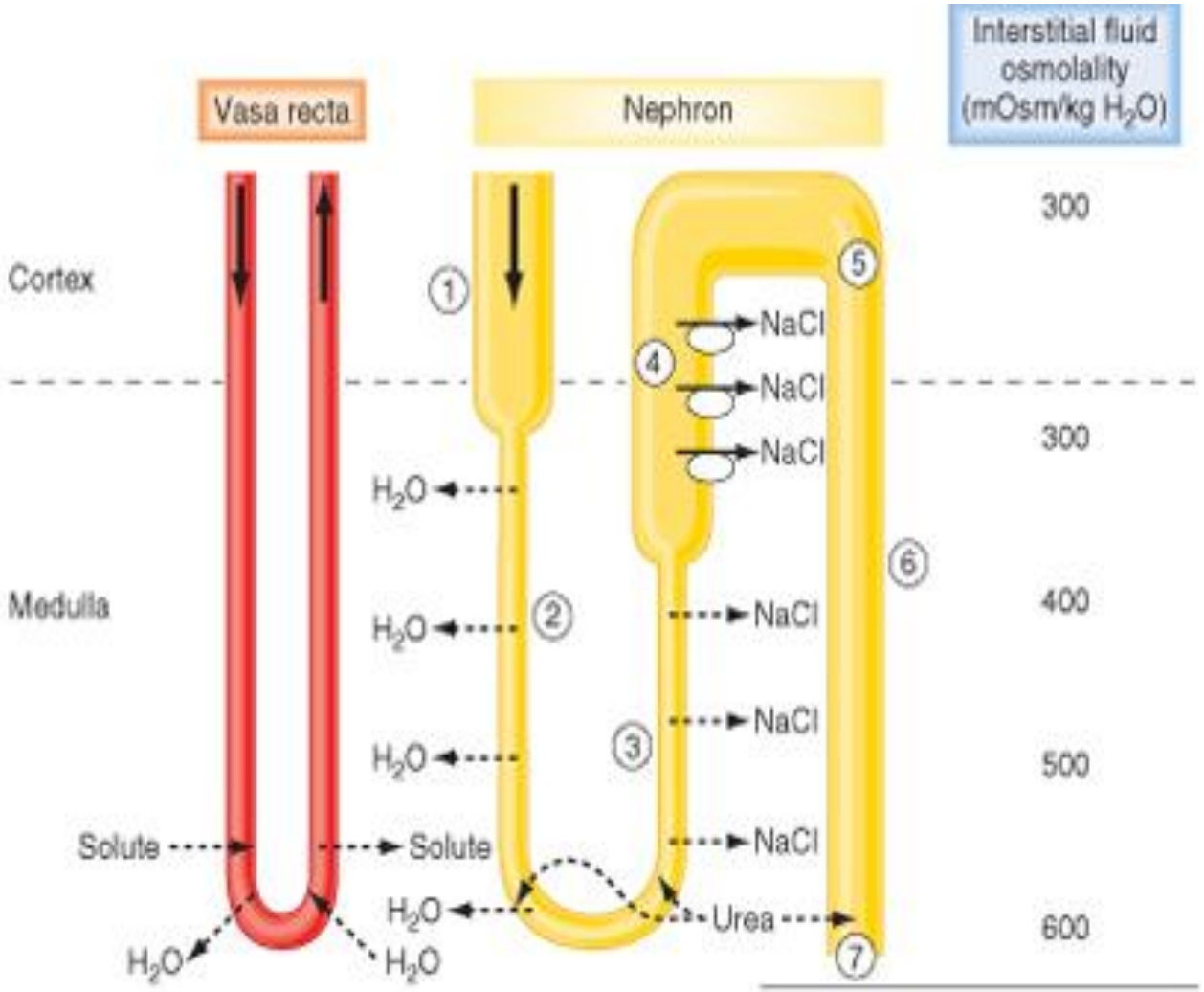
Concentrated Urine

Concentration of urine *(ADH dependent)*: "The first 4 steps are the same of diluted urine"



- When ADH levels high urea levels in medullary collecting duct and interstitium *equilibrate.*
- Most of water reabsorbed in the *cortical collecting duct.*

- Late CD is the site where urea will be absorbed.
- in step 5, ADH will start to work and absorb water so the conc. of urine will increase
- The osmolarity in interstituim is high because the change of the osmolarity of the whole body due to ADH


Vasa recta
Nephron
Interstitial fluid osmolality (mOsm/kg H_2O)
Cortex
Medulla
300
300
400
500
600
NaCl
NaCl
NaCl
NaCl
NaCl
NaCl
H_2O
H_2O
H_2O
H_2O
H_2O
H_2O
Solute
Solute
Urea
1
2
3
4
5
6
7

EXTRA

• Guyton corner :

Requirements for Excreting a Concentrated Urine—High ADH Levels and Hyperosmotic Renal Medulla
The basic requirements for forming a concentrated urine are (1) a high 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, and (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 high levels of ADH.

The renal medullary interstitium surrounding the collecting ducts is normally hyperosmotic, so 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. Thus, the urine concentrating ability is limited by the level of ADH and by the degree of hyperosmolarity of the renal medulla. We discuss 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 the human, about 25 percent 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.

- **Guyton corner :**

Role of Distal Tubule and Collecting Ducts in Excreting 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 dilute, with an osmolarity of only about 100 mOsm/L (Figure 28-5). 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 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 small compared with that added to the cortex interstitium. The reabsorbed water is quickly carried away by the vasa recta into the venous blood. When high levels of ADH are present, the collecting ducts become permeable to water, so 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 (see Figure 28-4). Thus, by reabsorbing as much water as possible, the kidneys form 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.

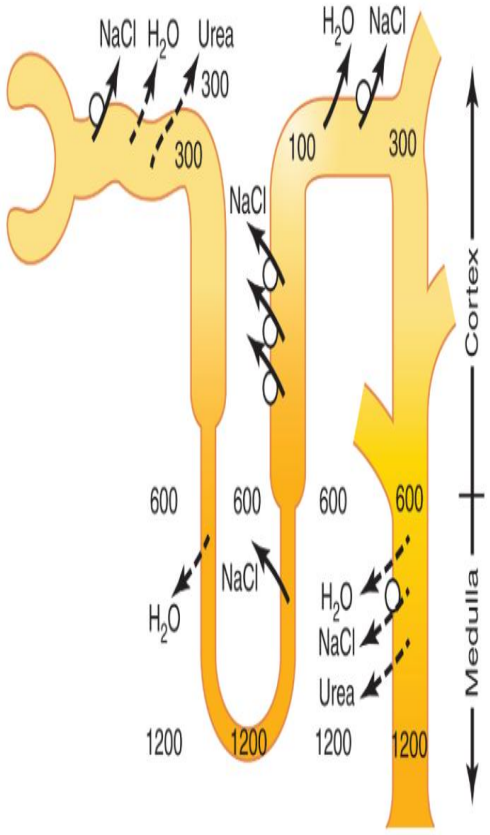


Figure 28-5

EXTRA

- **Guyton corner :**

Urea Contributes to Hyperosmotic Renal Medullary Interstitium and Formation of Concentrated Urine

Thus far, we have considered only the contribution of sodium chloride to the hyperosmotic renal medullary interstitium. However, urea contributes about 40 to 50 percent of the osmolarity (500 to 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 concentration of ADH is high, large 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: 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 (see Table 28-1). 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.

As the tubular fluid flows into the inner medullary collecting ducts, still more water reabsorption takes place, causing an even higher concentration of urea in the fluid. 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 interstitial fluid. This diffusion is greatly facilitated by specific *urea transporters, UT-A1 and UT-A3*. One of these urea transporters, UT-A3, is activated by ADH, increasing transport of urea out of the inner medullary collecting duct even more when ADH levels are elevated. 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 fundamental role of urea in contributing to urine concentrating ability is evidenced 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.

Table 28-1 : go back to slide 5

- **Guyton corner :**

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

A healthy person usually excretes about 20 to 50 percent 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 and (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.In the proximal tubule, 40 to 50 percent 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 (Figure 28-6). The passive secretion of urea into the thin loops of Henle is facilitated by the urea transporter *UT-A2*.The thick limb of the loop of Henle, the distal tubule, and the cortical collecting tubule are all relatively impermeable to urea, and very little urea reabsorption occurs in these tubular segments. When the kidney is forming concentrated urine and high levels of ADH are present, reabsorption of water from the distal tubule and cortical collecting tubule further raises the tubular fluid concentration of urea. 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 and then 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. This urea recirculation provides an additional mechanism for forming a hyperosmotic renal medulla. 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, urine flow rate is usually increased and therefore the concentration of urea in the inner medullary collecting ducts is reduced, causing less diffusion of urea into the renal medullary interstitium. ADH levels are also reduced when there is excess body water and this, in turn, decreases the permeability of the inner medullary collecting ducts to both water and urea, and more urea is excreted in the urine.

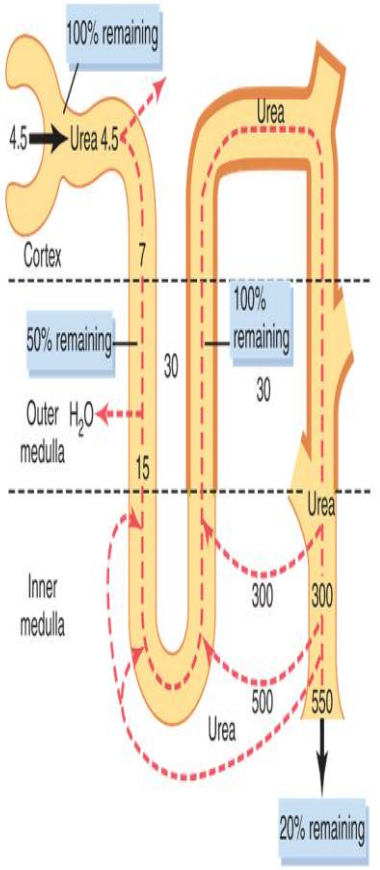


Figure 28-6

Vasa Recta

- **There are two special features of the renal medullary blood flow that contribute to the preservation of the high solute concentration:**

The medullary blood flow is low, accounting for *less than 5%* of the 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

The vasa recta serve as *countercurrent exchanger,* minimizing washout of solutes from the medullary interstitium.

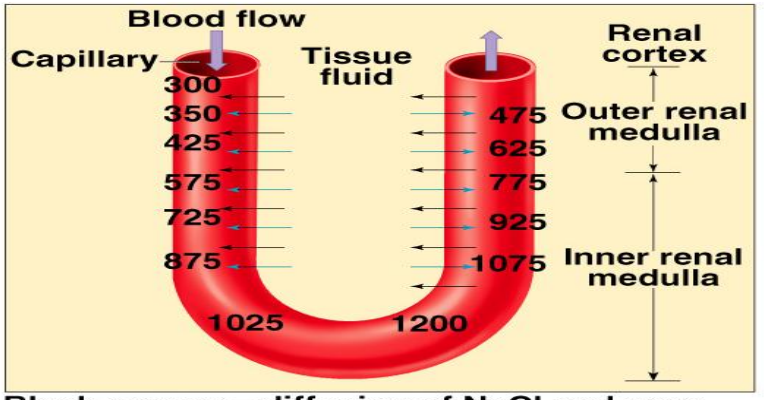
The vasa recta do not create the medullary hyperosmolarity but they do prevent from being dissipated (very important!!)

Vasa Recta

- Vasa recta *maintains* hypertonicity by *countercurrent exchange.*

Properties :

- Recycles NaCl in medulla.
- Transports H_2O from interstitial fluid.
- Descending limb:
  - Urea transporters.
  - Aquaporin proteins (H20 channels).
- Ascending limb:
  - Fenestrated capillaries.



Black arrows = diffusion of NaCl and urea
Blue arrows = movement of water by osmosis

- NaCl and urea diffuse into descending limb and diffuse back into medullary tissue fluid.
- At each level of the medulla , solute is higher in the ascending limb than in the interstitial Fluid and higher in the interstitial fluid than in descending vessels.
- Walls are *permeable* to H_20, NaCl and urea.
- Colloid osmotic pressure in vasa recta > interstitial fluid.

- **Guyton corner :**

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 dissipated.

There are two special 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 percent 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 (Figure 28-7): Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla. The vasa recta, like other capillaries, are highly permeable to solutes in the blood, except for the plasma proteins. 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. 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. 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.

Although there are large amounts 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. *Thus, the vasa recta do not create the medullary hyperosmolarity, but they do prevent it from being dissipated.*

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. 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 preserved.

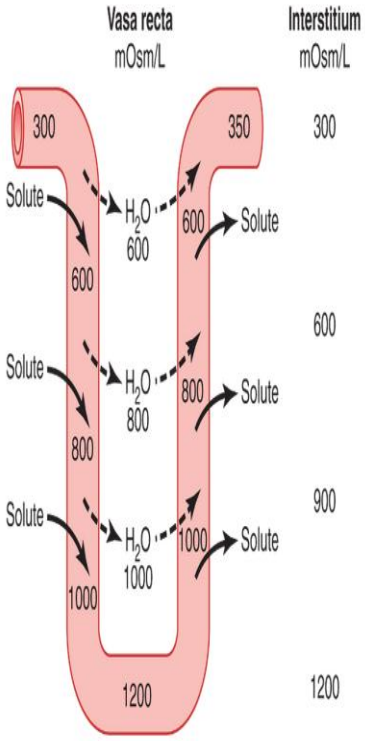
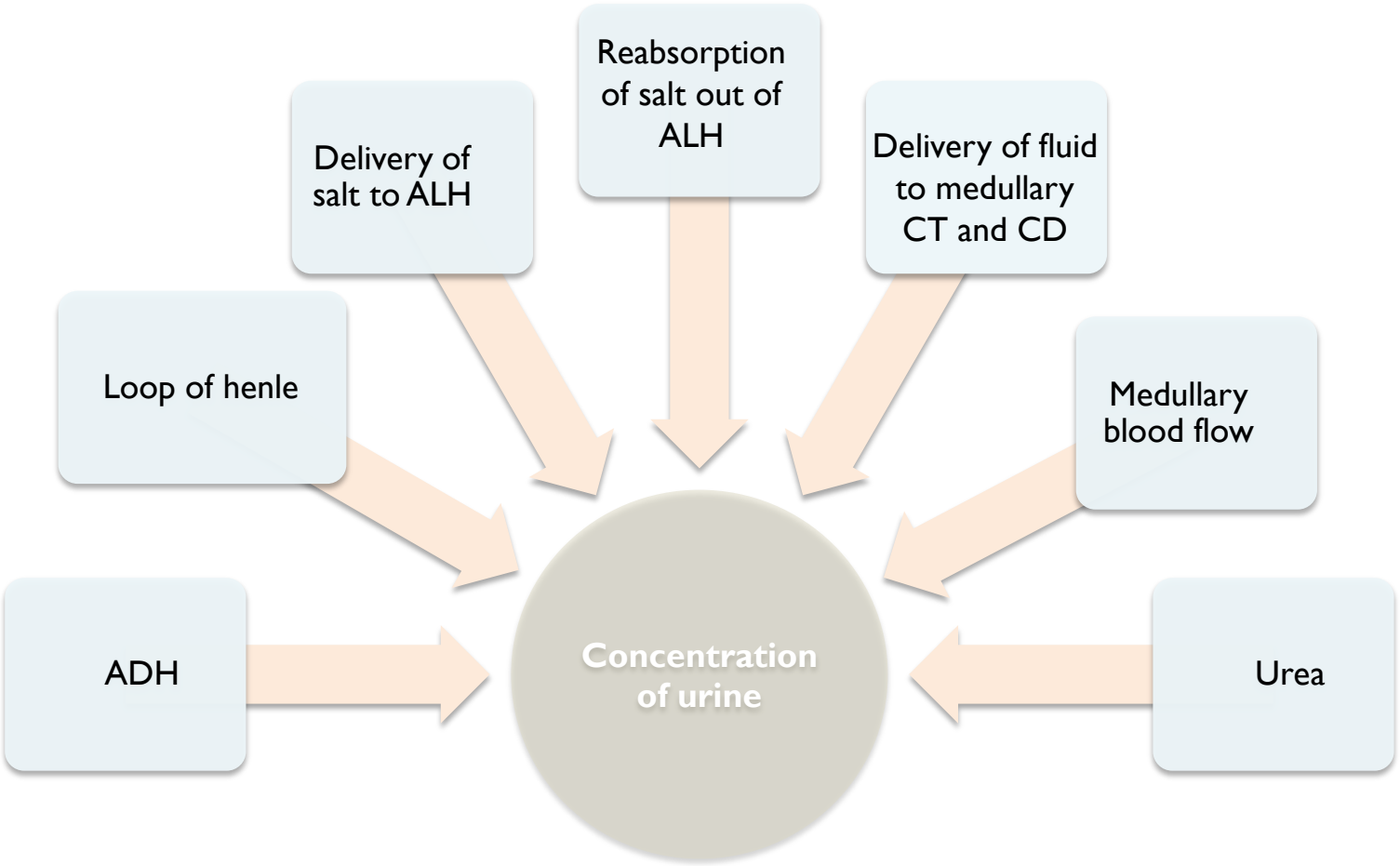


Figure 28-7

EXTRA

Deference between counter current systems			
System	**Site**	**Function**	**Type of Transport**
Countercurrent Multiplier	In loop of Henle	Produce medullary hyperosmolaraty	Active trasport
Countercurrent Exchanger	In vasa recta	Maintain medullary hyperosmolaraty	Passive transport

Factors affecting urine concentration



ALH : Ascending loop of henle

Factors affecting urine concentration

Factors affecting urine concentration	
1	**ADH:** causes an increase in permeability of DCT, CT, and CD for water. It also increases the permeability of medullary CD to urea.
2	**Length of the loop of Henle:** *the longer the loop of Henle, the greater the countercurrent multiplication effect and more urine concentration.* The new born baby having shorter loop of Henle can not concentrate as same as the adult.
3	**Delivery of salt to Ascending loop of henle:**

due to a decrease in GFR (Hemorrhage) the filter load of solute is decreased → decrease in the delivery of salt to ALH resulting in decreased reabsorption of salt from ALH. → decreased addition of salts to the medullary ISF → decreased medullary longitudinal osmotic gradient and decreased urine concentration.

ISF : interstitial fluid

Factors affecting urine concentration

Cont.

Factors affecting urine concentration	
4	**Delivery of fluid to medullary CT and CD:** • Maximum urine concentration occurs when only a small amount of fluid enters the medullary CT and CD. • Even during an osmotic diuresis, the increased fluid volume delivered to the medullary CT and CD leads to wash out of medullary longitudinal osmotic gradient and cause decreased urine concentration.
5	**Reabsorption of salt out of ALH** *(check the diagram below)*

Diuretic drugs (Lasix) prevents NaCl reabsorption from thick ALH → decreased addition of salts to the medullary ISF → decreased medullary longitudinal osmotic gradient and finally decreased urine concentration

Factors affecting urine concentration

Cont.

Factors affecting urine concentration	
6	**Medullary blood flow:** • Normally very low blood flow (about 5% of total RBF) to the medulla. • Increased blood flow to the medulla may cause wash out of the medullary longitudinal osmotic gradient, decreased effectiveness of the countercurrent exchange system and decreased urine concentration
7	**Urea:** • Urea recycling contributes significantly to the medullary longitudinal osmotic gradient and is essential for the countercurrent system. • A person on a protein free diet loses the ability to concentrate urine due to lack of urea in the medulla.

- **Guyton corner :**

Increased Medullary Blood Flow Reduces 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. As discussed earlier, 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.

Water Diuresis and Osmotic Diuresis

Water diuresis	Osmotic diuresis
Increased urine flow rate (No change in urine excretion of solutes)	Increase urine flow rate as well as the excretion of solutes
Causes: - Excess ingestion of water - Lack of ADH - Defect in ADH receptors in Distal segment of nephron (nephrogenic Diabetes Insipidus)	**Causes:** - Increase plasma glucose level (DM) - Increase level of poorly reabsorbed solutes/ anions - Diuretic drugs (Lasix)
• Diuresis is mainly due to decrease in water reabsorption in distal segment of nephron. No change to the water reabsorbed proximally	• Diuresis is mainly due to decrease reabsorption of solute in PCT or LOH. • Decrease solute reabsorption results in decrease in water reabsorption proximally as well as distally.

Water Diuresis and Osmotic Diuresis

Water diuresis	Osmotic diuresis
Increase urine volume results from increased excretion of pure water	Increase urine volume results from increased excretion of osmotically active solutes which pulls water with it.
Urine osmolality falls far below plasma osmolality.	Urine osmolality falls but remains above plasma osmolality.
Only about 15% filtred load of water reaching distal segments may remain **unabsorbed** and excreted in urine (maximum urine volume 20 ml/min)	Due to decreased water reabsorption in all segments of nephron, a much greater fraction of filtered water may be excreted volume **more** than 20 ml/min
ADH administration will stop diuresis if it is due to lack of ADH or excess ingestion of water. ADH administration will not be effective in Nephrogenic Diabetes Insipidus.	ADH administration will NOT stop diuresis.

Disorders of urinary concentrating ability

Diabetes insipidus

Cause:

inability to produce or release ADH

Urine:

- Low fixed specific gravity (diluted urine)
- Polyuria "abnormally large volumes of dilute urine"
- Polydipsia "Abnormal thirst"

Nephrogenic diabetes insipidus

Cause:

inability of kidney to respond to ADH

Diabetes mellitus

Urine:

High specific gravity urine

high specific gravity means that urine is concentrated due to glucose excretion in DM

- **Guyton corner :**

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. Inability of the distal tubule, collecting tubule, and collecting ducts to respond to ADH.

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, discussed later in this chapter, 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 (e.g., 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 it rapidly restores urine output toward normal. Inability of the Kidneys to Respond to ADH: "Nephrogenic" Diabetes Insipidus.In some circumstances 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. Also, impairment of the function of the loop of Henle, as occurs with diuretics that inhibit electrolyte reabsorption by this segment, such as furosemide, 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.

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

- **Guyton corner :**

Proximal Tubule.

About 65 percent of the filtered electrolytes is reabsorbed in the proximal tubule. However, the proximal 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 nearly equal to that of the surrounding interstitial fluid, which is about 1200 mOsm/L when the blood concentration of ADH is high.
When 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. Thus, 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 large 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.

Early Distal Tubule.

The early distal tubule has properties similar to those of the thick ascending loop of Henle, so further dilution of the tubular fluid to about 50 mOsm/L occurs as solutes are reabsorbed while water remains in the tubule.

Summary of Urine Concentrating Mechanism and Changes in Osmolarity in Different Segments of the Tubules (cont.)

- **Guyton corner :**

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 high 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 allows most of the urea delivered to the distal tubule and collecting tubule to pass into the inner medullary collecting ducts, from which it is eventually reabsorbed or excreted in the urine. In the absence of ADH, little water is reabsorbed in the late distal tubule and cortical collecting tubule; therefore, 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 and (2) the surrounding medullary interstitium osmolarity established 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 interstitial fluid until osmotic equilibrium is reached, with the tubular fluid having about the same concentration as the renal medullary interstitium (1200 to 1400 mOsm/L). Thus, a small volume of concentrated 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. This 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.Several important points to consider may not be obvious from this discussion. First, although sodium chloride is one of the principal solutes that contribute 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. One condition in which this occurs is dehydration accompanied by low sodium intake. low sodium intake stimulates formation of the hormones 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.Second, *large quantities of dilute urine can be excreted without increasing the excretion of sodium*. This is accomplished by decreasing ADH secretion, which reduces water reabsorption in the more distal tubular segments without significantly altering sodium reabsorption.And finally, there is an *obligatory urine volume* that 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. For example, if 600 milliosmoles of solute must be excreted each day, this requires *at least* 0.5 liter of urine if maximal urine concentrating ability is 1200 mOsm/L.

Summary of Urine Concentrating Mechanism and Changes in Osmolarity in Different Segments of the Tubules (cont.)

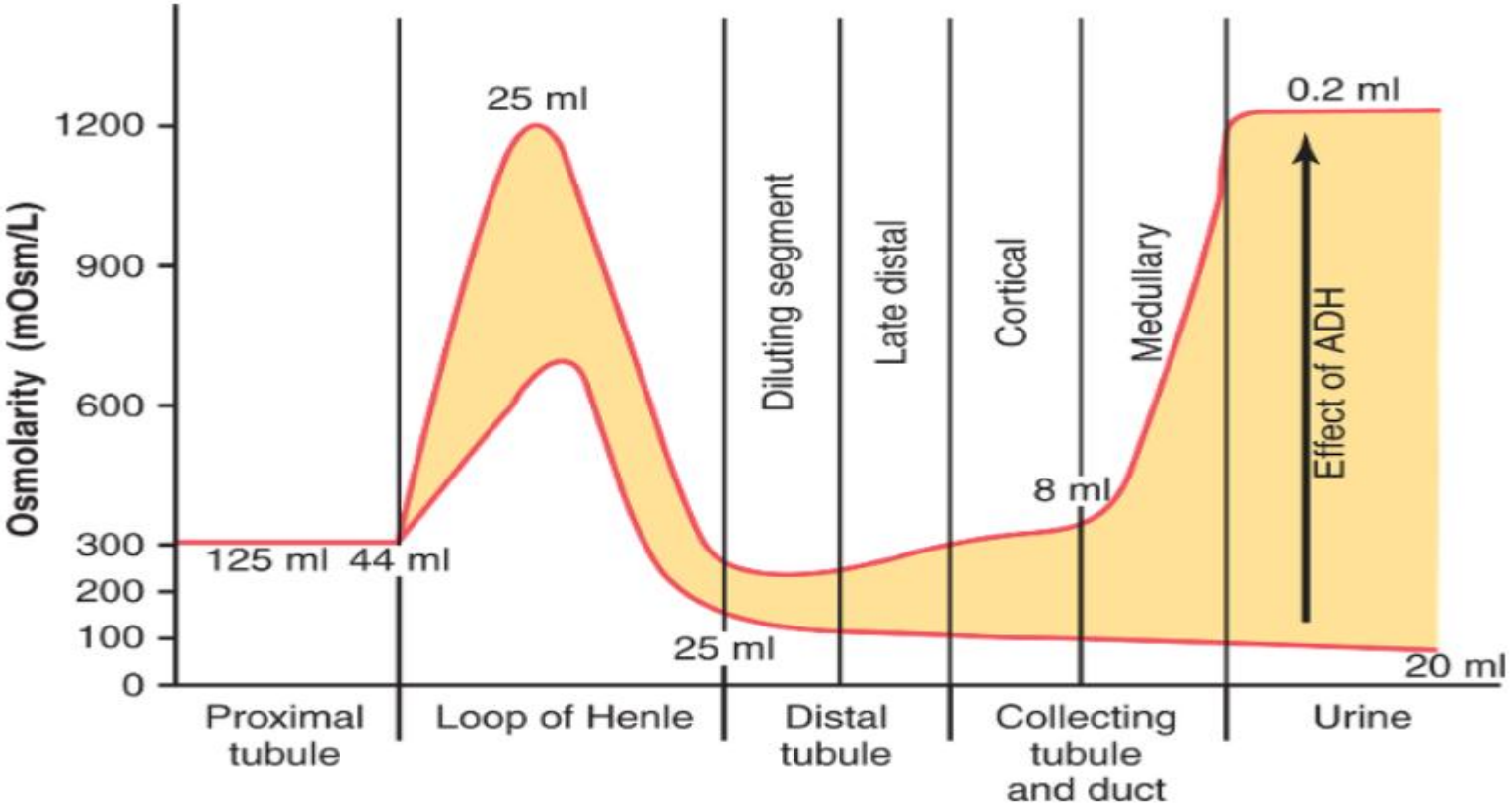


Figure 28-8

- **Guyton corner :**

The changes in osmolarity and volume of the tubular fluid as it passes through the different parts of the nephron are shown in Figure 28-8.

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