Sheet No.

Physiology

Genitourinary system

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Concentration and dilution of urine

Normal kidneys have a tremendous capability to vary the relative proportions of solutes and water in the urine. In the plasma, Na+ accounts for the majority of effective osmoles.

Plasma osmolarity = 2.1 * Na+ osmolarity = 300 mOsm/L

Regarding the previous equation, it's evident that Na+ osmolarity and its attendance contribute the majority of plasma osmolarity, while other solutes such as urea and glucose don't provide effective osmoles (as they're too large).

❖ **Control of extracellular osmolarity (NaCl concentration)**:

ADH and thirst are the main regulators of Na+ osmolarity, collectively referred to as ADH-Thirst osmoreceptor system.

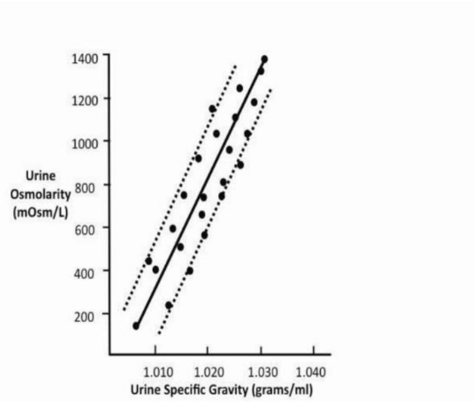
Mechanism: increased extracellular osmolarity (NaCl) stimulates ADH release, which increases H_2O reabsorption, and stimulates thirst (intake of water) and vice versa. It's essential to maintain a normal plasma osmolarity to avoid shrinkage or swelling of cells as well as avoiding changes in blood volume and electrolytes balance.

When there is excess water in the body and body fluid osmolarity is reduced, the kidneys can excrete urine with an osmolarity **as low as 50-70 mOsm/L {Minimal urine concentration}**. Conversely, when there is a deficit of water in the body and extracellular fluid osmolarity is high, the kidneys can excrete **highly concentrated urine with an osmolarity of 1200 to 1400 mOsm/L {Maximal urine concentration}**. Equally important, the kidneys 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.

❖ **Relationship between urine osmolarity and specific gravity:**

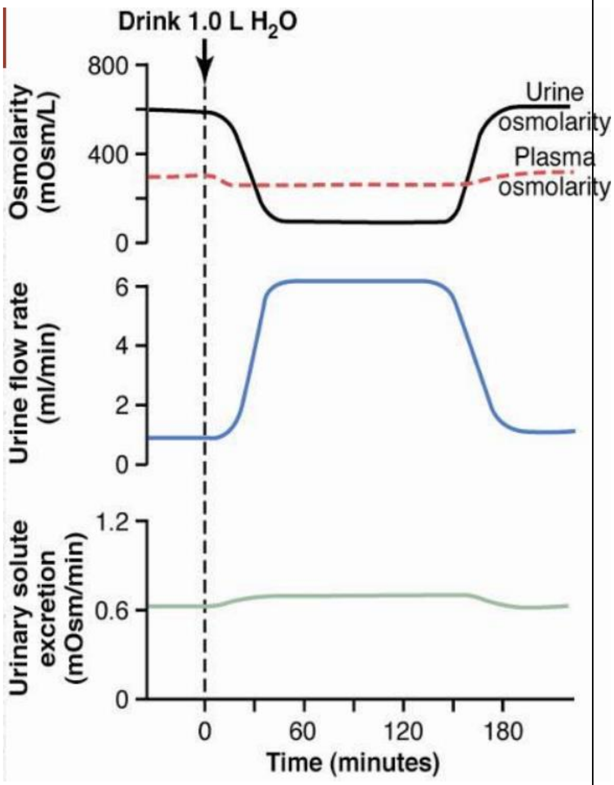
Specific gravity is a measure of the **weight** of solutes in a given volume of urine and is therefore determined by the size of the solute molecules. In contrast, osmolarity is determined only by the **number** of solute molecules in a given volume.

Normally, at the minimal urine concentration (50-70 mOsm/L), the specific gravity measures around **1.003** while at the maximal urine concentration (1200-1400 mOsm/L), the specific gravity measures around **1.030** . In abnormal conditions, the specific gravity can be misleading if abnormal substances are present such as glucose, proteins, antibiotics, and contrast media.



e.g. diabetics can have a normal specific gravity of 1.030 while not having a plasma osmolarity of 1400 mOsm/L due to the presence of glucose in the urine which carries a large molecular weight. (Notice the right shifting of the curve indicating an increase in the specific gravity).

- An experiment of ingestion of 1 liter of water and tracing the osmolarity (black) mOsm/L, plasma osmolarity(red) mOsm/L, urine flow rate (blue) ml/min, urinary solute excretion (green) mOsm/min over a period of time:

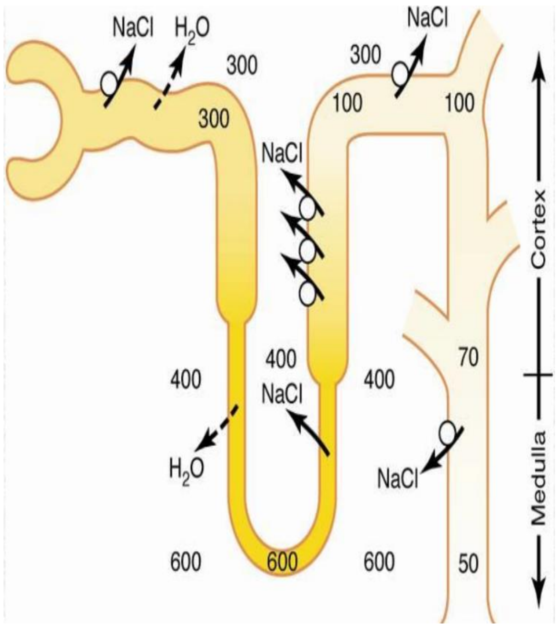


- In the first graph, after 30-45min from ingestion, urine concentration (urine osmolarity) drops, at the same time in the second graph urine flow rate increases 6 times the original flow rate and then they both return to the normal rate within 1-2 hrs.
- In the last graph, urinary solute excretion doesn't change.
- Keep in mind that **ADH is the main regulator of plasma osmolarity**. So, increasing the water intake will inhibit ADH which will affect only water excretion and doesn't affect urinary solute excretion.
- Urine dilution is due to decreased water reabsorption NOT due to increased solutes reabsorption.

- **Formation of a dilute urine:**

Is produced when circulating levels of ADH are low causing reduced water permeability in the late distal and collecting tubules. Therefore, the decreased water reabsorption coupled with continual electrolyte reabsorption leads to the formation of dilute urine.

1. Filtered fluid from the glomerulus flows to the bowman's capsule. Tubular osmolarity = plasma osmolarity =300mOsm/L.
2. Tubular fluid flows to the proximal tubule; reabsorption of solutes and water happened, so the ratio between tubular osmolarity and plasma osmolarity =1.
3. Thin descending Henle; which is permeable to water. **As we go down from the cortex to the medulla, interstitial osmolarity increases from 300 to 400 to 600, so tubular osmolarity will increase too (equilibrium).**
4. Thin Ascending Henle; impermeable to water, permeable to solutes mainly NaCl. As we go up from medulla to cortex, interstitial osmolarity decrease from 600 to 400 to 200 so, tubular osmolarity will decrease too (Start dilution).



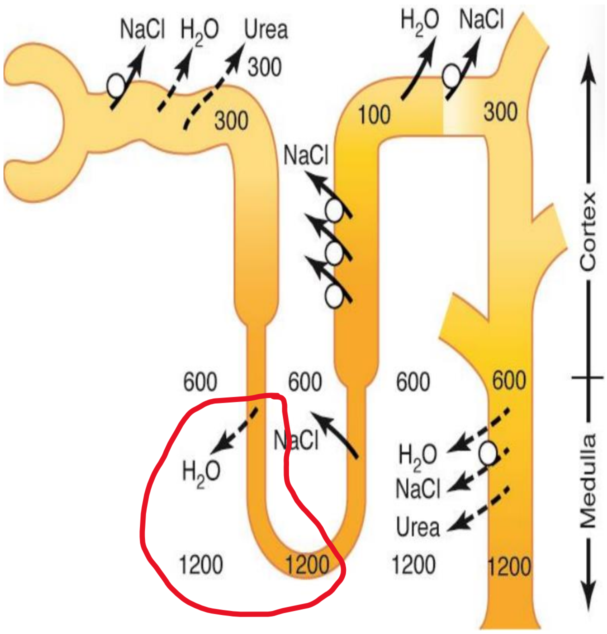
5. Thick Ascending Henle; impermeable to water, active reabsorb of solutes mainly NaCl. Tubular osmolarity reaches 100mOsm/L which is very diluted.
6. Early distal; impermeable to water, continuous reabsorption of the solutes actively.
7. Late distal and collecting tube; its permeability to water variable and depends on ADH, and here we have high water volume, ADH is absent. So, it's impermeable to water but the reabsorption of the solutes will continue actively, so more urine dilution until tubular osmolarity reaches 50mOsm/L with a huge volume of urine.

❖ **Formation of a Concentrated Urine when antidiuretic hormone (ADH) are high:**

When there is a deficit of the water in the body either because of low intake or high loss (Sweating, high expiration rate, Diarrhea, hemorrhage), the kidney will continue electrolyte reabsorption and increase water reabsorption. This happened in the presence of ADH. So, conserve the amount of the water without affecting the solutes excretion.

Mechanism:

- ✓ Increased ADH release which increases water permeability in distal and collecting tubules
- ✓ High osmolarity of renal medulla: most of H2O is reabsorbed before reaching the inner medulla accordingly this will maintain a high interstitial osmolarity (1200 mOsm/L). This will facilitate urine concentration.
- ✓ Countercurrent flow of tubular fluid is largely responsible for developing the osmotic gradients that are needed to concentrate urine.



Regarding the figure:

1. Thin descending Henle: passive water reabsorption to reach equilibrium, TO=IO=1200mOsm/L.
2. Thin Ascending Henle: passive solutes reabsorption to reach equilibrium, dilution in the tubular fluid, TO=IO=600 mOsm/L.
3. Thick Ascending Henle: reabsorption of solutes **actively**, more dilution in the tubular fluid, TO=100 mOsm/L.
4. Late distal and cortical collecting tube; **its permeability to water is variable and depends on ADH**, and here we have low water volume, so stimulation of ADH release thus increases aquaporin insertion which increases water permeability in late distal and cortical collecting tubules, so concentrating the urine.
5. In the medullary collecting tubules: ADH increases urea transporter insertion, so reabsorption to urea down their gradient, which will increase the urea concentration in the interstitium, thus increasing the interstitial osmolarity and increasing the kidney's ability to concentrate urine.

- **Note regarding point 5**: individuals with protein malnutrition will have low levels of urea and therefore interstitial osmolarity will not reach its highest level thus interfering with urine concentrations.

- **Obligatory urine volume:** the minimum urine volume in which the excreted solute can be dissolved and excreted.

Example: If the max. urine osmolarity is 1200 mOsm/L, and 600 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is:

$$\frac{600 \text{ mOsm/d}}{1200 \text{ mOsm/L}} = 0.5 \text{ L/day}$$

In renal disease the obligatory urine volume may be increased due to impaired urine concentrating ability.

Example: If the max. urine osmolarity = 300 mOsm/L, and 600 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is:

$$\frac{600 \text{ mOsm/d}}{300 \text{ mOsm/L}} = 2.0 \text{ L/day}$$

- **Factors That Contribute to Buildup of Solute in Renal Medulla - Countercurrent Multiplier:**

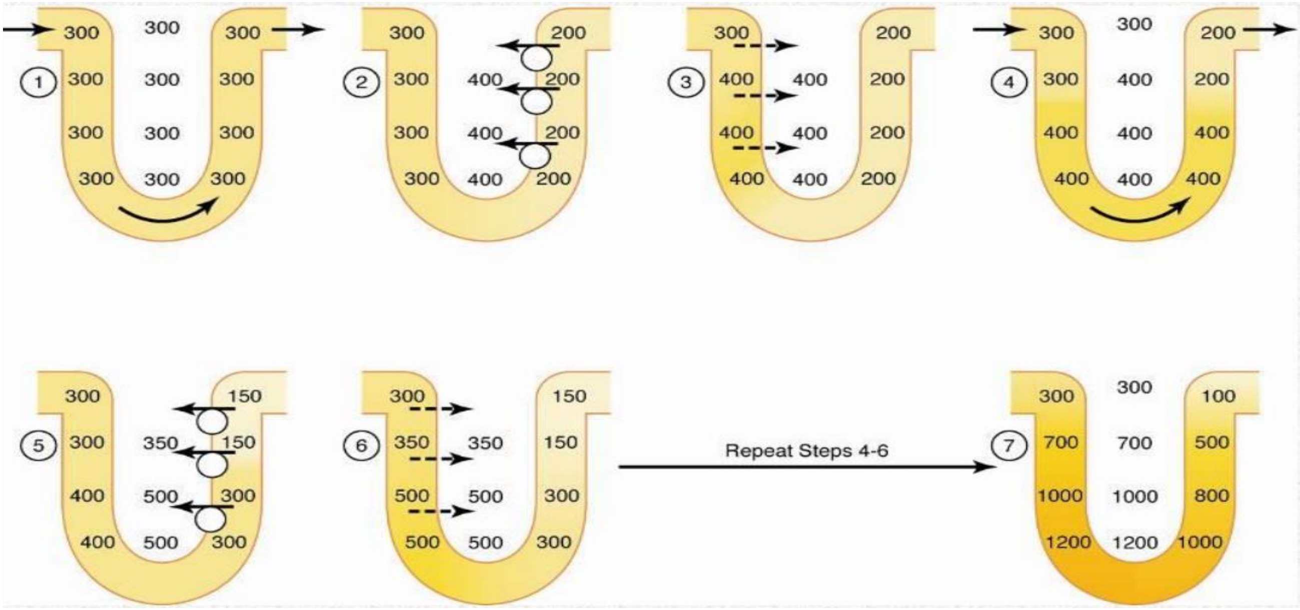
1. Active transport of Na+ , Cl- , K+ and other ions from thick ascending loop of Henle into medullary interstitium.
2. Active transport of ions from medullary collecting ducts into interstitium.
3. Passive diffusion of urea from medullary collecting ducts into interstitium .
4. Diffusion of only small amounts of water into medullary interstitium.

- **Summary of Tubule Characteristics:**

		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

- Notice at the level of TDL and TAL, there is some permeability for urea as urea is present at higher concentrations in the interstitiam causing the secretion of urea.

❖ **Countercurrent multiplier system in the loop of Henle:**



1) Assume that the loop of Henle is filled with fluid with a concentration of 300mOsm/L, the same as that leaving the proximal tubule, the interstitial fluid concentration also 300mOsm/L, so we have equilibrium (zero point). Remember, we don't have zero points in our bodies but it's an experimental assumption.

2) The active ion pump of the thick ascending limb on the loop of Henle reduces the concentration inside the tubule to 200mOsm/L and raises the interstitial concentration to 400mOsm/L; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid. The limit to the gradient is about 200mOsm/L because paracellular diffusion (leaking) of ions back into the tubule eventually counterbalances the transport of ions out of the lumen when the 200mOsm/L concentration gradient is achieved.

3) The descending limb of the loop of Henle is permeable to water so, tubular fluid in the descending limb and the interstitial fluid quickly reaches an osmotic equilibrium of 400mOsm/L.

4) The additional flow of fluid into the loop of Henle from the proximal tubule causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb.

5) Once this fluid is in the ascending limb, additional ions are pumped into the interstitium, with water remaining in the tubular fluid, until a 200mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity rising to 500mOsm/L.

6) These steps are repeated over and over, with the net effect of adding more and more solutes to the medulla; 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.

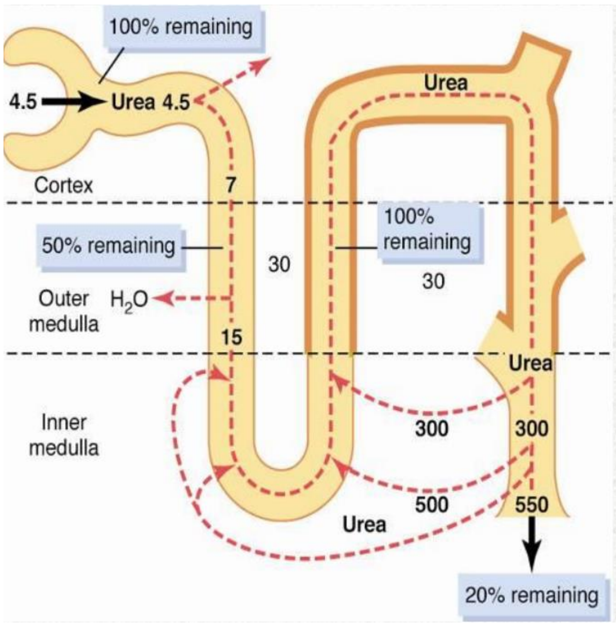
- This Countercurrent multiplier system in the loop of Henle is accompanied by **Vasa recta**.

Net effects of countercurrent multiplier:

- ✓ More solute than water is added to the renal medulla. i.e solutes are "trapped" in the renal medulla.
- ✓ Fluid in the ascending loop is diluted.
- ✓ Most of the water reabsorption occurs in the cortex (i.e. in the proximal tubule and in the distal convoluted tubule) rather than in the medulla.
- ✓ Horizontal gradient of solute concentration established by the active pumping of NaCl is "multiplied" by countercurrent flow of fluid.

❖ Recirculation of urea absorbed from medullary collecting duct into interstitial fluid:

In the proximal tubule, 50% of the filtered urea is reabsorbed. Once urea reaches the thin descending limb, the extensive reabsorption of water concentrates urea even more. At the level of thin and thick ascending limbs, there is extensive secretion of urea from the inner medullary interstitiam (which has a high concentration of urea) toward the tubule. This along with the impermeability of water in the ascending limbs causes urea's concentration to return back to 100%.



Urea remains unchanged throughout the distal tubule and cortical collecting tubule. After reaching the medullary collecting tubule, extensive reabsorption of urea takes place leaving 20% to be excreted.

Note: among the 80% of urea reabsorbed, 50% will undergo secretion from inner medullary interstitiam toward the ascending and descending limbs while 30% of urea remains in the interstitiam.

❖ **Urea Recirculation (Summary)**

- Urea is passively reabsorbed in proximal tubule (~ 50% of filtered load is reabsorbed)
- In the presence of ADH, water is reabsorbed in distal and collecting tubules, concentrating urea in these parts of the nephron.
- **The inner medullary collecting tubule is highly permeable to urea, which diffuses into the medullary interstitium.**
- ADH increases urea permeability of medullary collecting tubule by activating urea transporters (UT-1).

❖ **The Vasa Recta Preserve Hyperosmolarity of Renal Medulla**

Mechanism:

(In the proximal part)

The juxtamedullary nephrons have a special arrangement of peritubular capillaries (vasa-recta) which are arranged parallel to each segment of the tubules. Reabsorption of solutes towards vasa recta increases because the osmolarity of the interstitium is higher than that of vasa recta. At the same time, due to the hyperosmotic interstitium, water will come out from vasa recta towards the hyperosmotic interstitum.

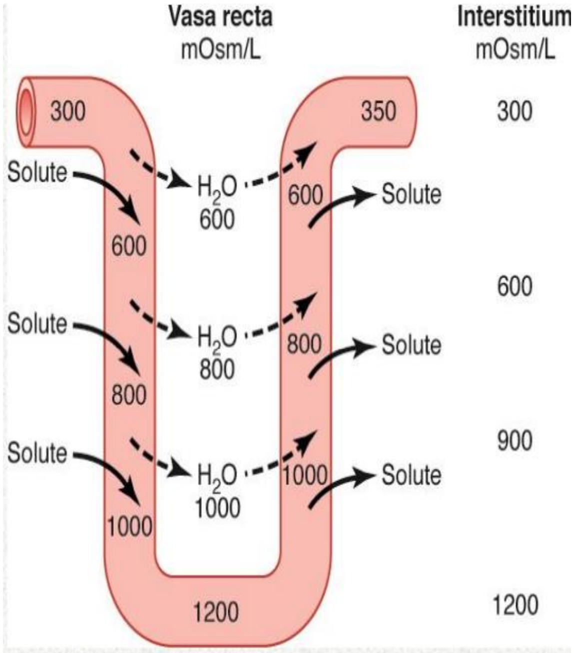


Figure 28-7

(In the ascending part of vasa recta)

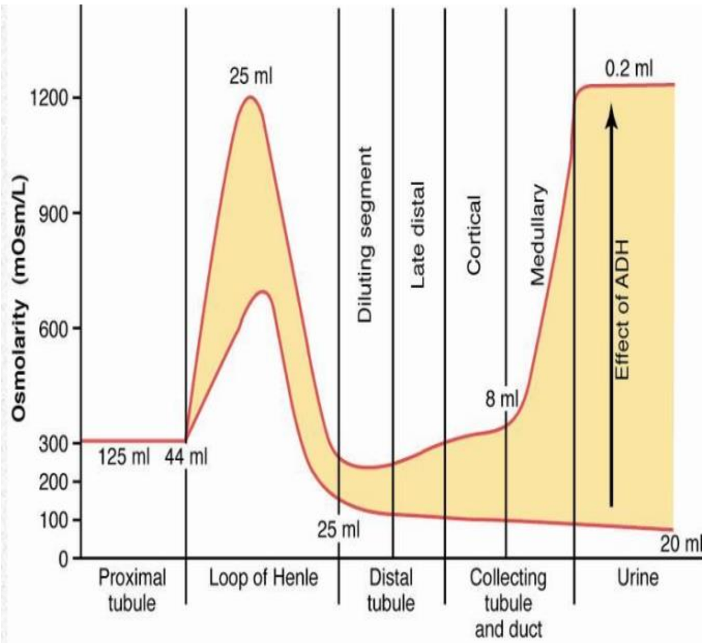
The solute is more concentrated inside the blood in comparison to the interstitum, and accordingly the same amount of solutes that entered the vasa recta in the previous segment, will reenter the insterstium again and the same amount of water that left the vasa recta towards the interstitum will return back to the vasa recta.

Thus, there is no net change in solute or water in the blood or the interstitum. However, a slight increase in reabsorption occurs as a result of paracellular diffusion (This slight increase won't affect the gradient (300 – 350) and will not cause a significant increase in the blood).

- Therefore, the vasa recta preserve the hyperosmolarity of the medulla without causing a change in the number of effective osmoles in the interstitum or the vasa recta.
- The vasa recta serve as countercurrent exchangers because they don't multiply the gradient of the interstitum and don't dilute the interstitum.
- Vasa recta flow is low especially in the medulla (only 1-2 % of total renal blood flow).

❖ Changes in osmolarity of the tubular fluid:

In this figure, we can notice an increase in the osmolarity of urine from 300 to 1200 and a decrease in the volume of urine from 125 ml/min in the proximal convoluted tubule to 0.2 ml/min.



Remember that the process of water reabsorption in different segments aids in the concentration of urine. However, the highest impact is in the late distal tubule, cortical and medullary collecting tubules by increasing the osmolarity because of the presence of ADH, UREA reabsorption and the counter transporter exchanger mechanism.

Summary of the figure:

- Proximal Tubule: 65 % reabsorption, isosmotic.
- Desc. loop: 15 % reabsorption, osmolarity increases.
- Asc. loop: 0 % reabsorption, osmolarity decreases.
- Early distal: 0 % reabsorption, osmolarity decreases.
- Late distal and coll. tubules: ADH dependent water reabsorption and tubular osmolarity
- Medullary coll. ducts: ADH dependent water reabsorption and tubular osmolarity

❖ "Free" Water Clearance (CH2O) (rate of solute-free water excretion):

Rate of solute-free water excretion, where high Clearance indicates **diluted** urine and low Clearance indicates **concentrated** urine.

If: Uosm < Posm, CH2O = positive → dilution

If: Uosm > Posm, CH2O = negative → concentration

$$CH_2O = V - \frac{Uosm \times V}{Posm}$$

where:

Uosm = urine osmolarity

V = urine flow rate

P = plasma osmolarity

If: Uosm < Posm, CH_2O = +

If: Uosm > Posm, CH2O = –

Question: Given the following data, calculate " free water" clearance : urine flow rate = 6.0 ml/min urine osmolarity = 150 mOsm /L plasma osmolarity = 300 mOsm / L Is free water clearance in this example positive or negative ?

$$CH_2O = V - \frac{Uosm \times V}{Posm}$$

$$= 6.0 - \frac{(150 \times 6)}{300}$$

$$= 6.0 - 3.0$$

$$= +3.0 \text{ ml / min (positive)}$$

❖ **Disorders of Urine Concentrating Ability**

- **Failure to produce ADH**: "Central" diabetes insipidus.

- **Failure to respond to ADH**: "nephrogenic" diabetes insipidus. Caused by:

- impaired loop NaCl reabsorption. (Loop diuretics).

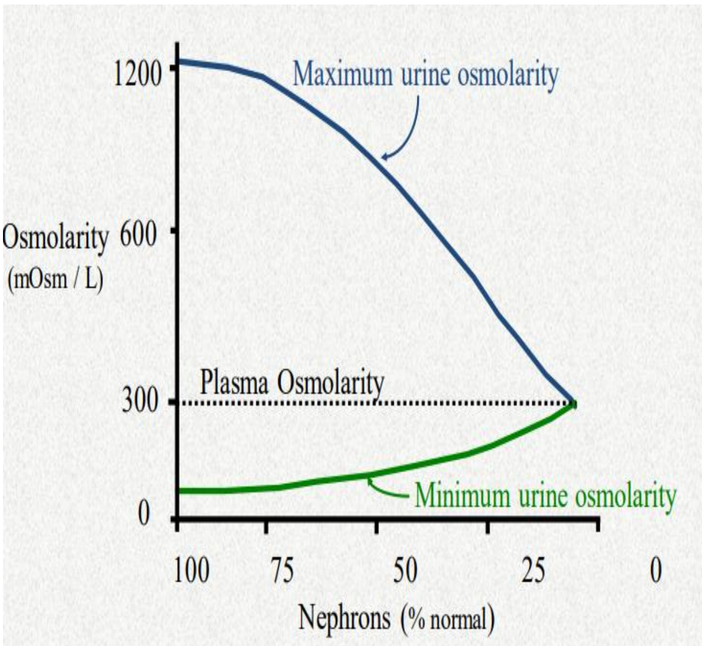
- drug induced renal damage: lithium, analgesics.

- kidney disease: pyelonephritis, hydronephrosis, chronic renal failure

- malnutrition (low protein intake = decreased urea concentration).

❖ **Development of Isosthenuria with Nephron Loss in Chronic Renal Failure (inability to concentrate or dilute the urine).**

As we go to the right on the x-axis, there is a decrease in the proportion of the normal nephrons due to chronic renal failure. As the proportion of the normal nephrons decreases, the minimum, and maximum urine osmolarity decreases too. When the nephrons are 100% normal, the kidney can dilute urine as low as 50 mOsm/L, and concentrate urine as high as 1200 mOsm/L. When 20% damaged (80% normal), the minimum and maximum urine osmolarity become closer to the plasma osmolarity → **Isosthenuria.**



- ❖ **Total Renal Excretion and Excretion Per Nephron in Renal Failure.**

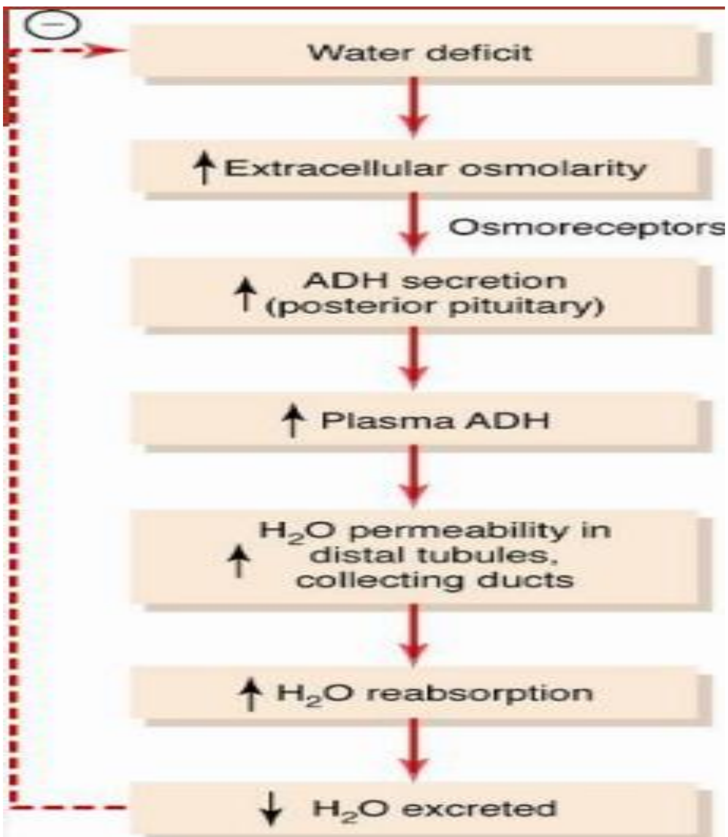
Note:

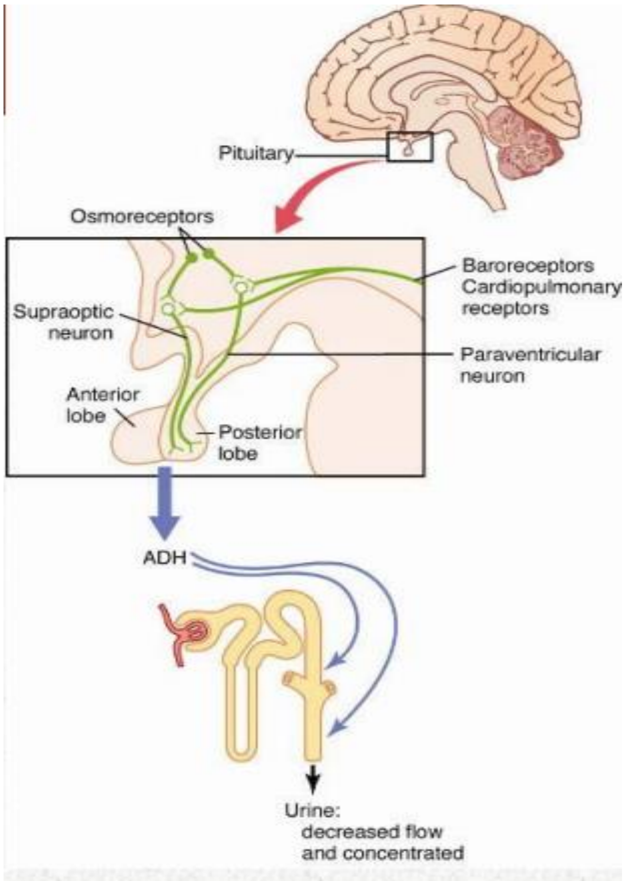
The process of concentration of urine will be affected by 75% loss of nephrons.

	Normal	75 % loss of nephrons
Number of nephrons	2,000,000	500,000
Total GFR (ml/min	125	40
GFR per nephron (nl/min)	62.5	80
Total Urine flow rate (ml/min)	1.5	1.5
Volume excreted per nephron (nl/min)	0.75	3.0

- ❖ **Osmoreceptor– antidiuretic hormone (ADH) feedback mechanism for regulating extracellular fluid osmolarity.**

Follow the sequence of events in the following graph (The doctor didn't mention anything extra).





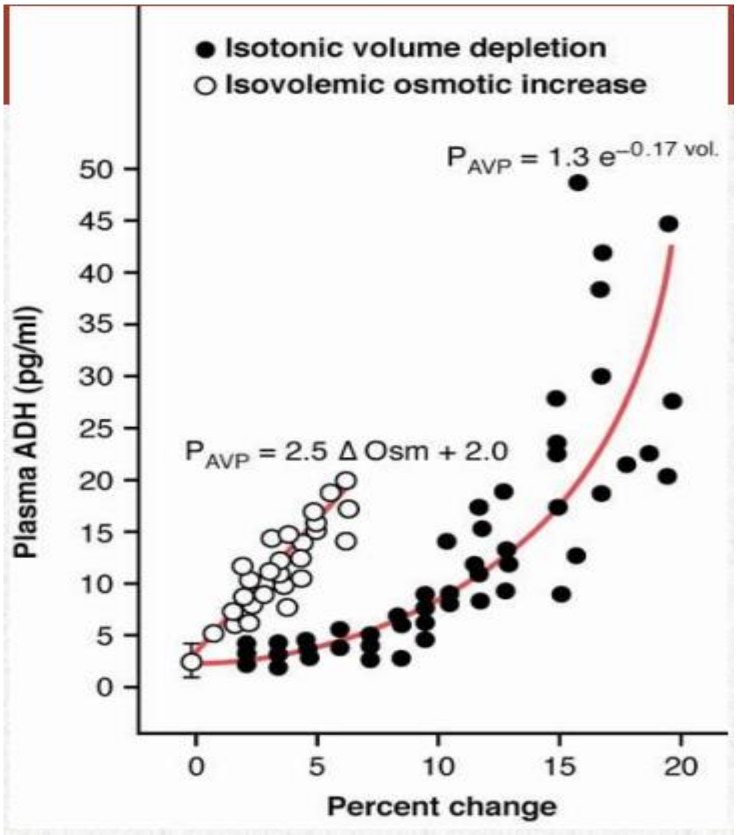
❖ **The effect of increased plasma osmolarity or decreased blood volume**

volume → decrease without changing the osmolarity.

osmolarity→ increase without changing the volume.

At low percent change (less than 5%) , the osmolarity will significantly increase plasma ADH, and this is much more than the effect of volume depletion.

After more than 10% percent change, volume depletion becomes a stronger stimulus than osmolarity and the effect becomes the highest after 15% change.



❖ **Maximal urine flow rate, water excretion rate**

- Maximal water excretion rate in adults = 20-23 L/day, does not exceed 800-1000 ml/hr.
- Water intake shouldn't exceed 800-1000 ml/ hr. **to avoid hyponatremia and water intoxication.**

❖ **ADH secretion:**

Stimuli for ADH Secretion

1. Increased osmolarity
2. Decreased blood volume (cardiopulmonary reflexes)
3. Decreased blood pressure (arterial baroreceptors)
4. Other stimuli:
   - input from the cerebral cortex (e.g., fear)
   - angiotensin II
   - nausea
   - nicotine
   - morphine

Factors That Decrease ADH Secretion

1. Decreased osmolarity
2. Increased blood volume (cardiopulmonary reflexes)
3. Increased blood pressure (arterial baroreceptors)
4. Other factors:
   - Alcohol
   - clonidine (antihypertensive drug)
   - haloperidol (antipsychotics, used to treat Tourette's syndrome)

❖ Thirst:

Stimuli for Thirst	Factors That Decrease Thirst
1. Increased osmolarity	1. Decreased osmolarity
2. Decreased blood volume(cardiopulmonary reflexes)	2. Increased blood volume (cardiopulmonary reflexes)
3. Decreased blood pressure(arterial baroreceptors)	3. Increased blood pressure(arterial baroreceptors)
4. Increased angiotensin II	4. Decreased angiotensin II
5. Other stimuli: - dryness of mouth	5. Other stimuli: - Gastric distention

THE END