

# Urine Concentration and Dilution; Regulation of Extracellular Fluid Osmolarity and Sodium Concentration. Chapter 28

Lecture-7 7/4/2015

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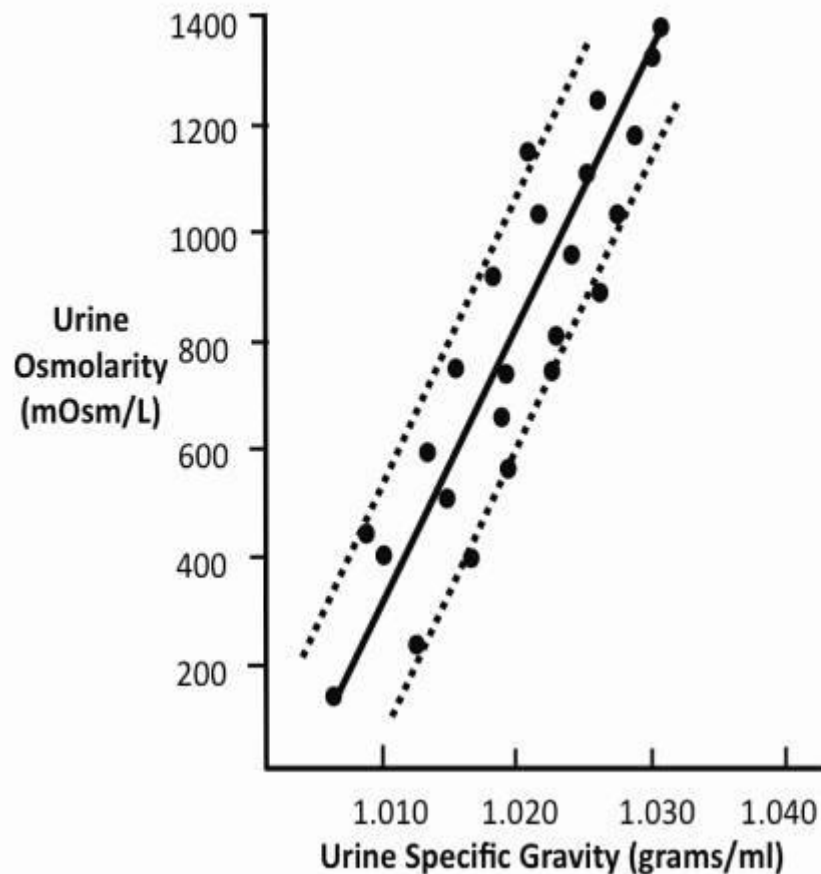
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- One of the most important tests is to look if the kidney can concentrate urine which is considered to be a tubular function**
- Urine specific gravity test ( it tests the ability of the kidneys to concentrate urine)**
    - ***High specific gravity means concentrated urine***
    - ***Low specific gravity means diluted urine***
    - **This is the last function to be retained following acute renal failure**
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# Concentration and Dilution of the Urine

- Maximal urine concentration  
= 1200 - 1400 mOsm / L  
(specific gravity ~ 1.030)
- Minimal urine concentration  
= 50 - 70 mOsm / L  
(specific gravity ~ 1.003)

# Relationship between urine osmolarity and specific gravity



## Influenced by

- glucose in urine
- protein in urine
- antibiotics
- radiocontrast media



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- Making concentrated urine means conservation of body water.
  - - Making diluted urine mean eliminating excess water.
  - **Observation:**
  - Only those species that have juxtamedullary nephrons (long loop of Henle) can make concentrated urine (desert rodents). While beaver with short loop of Henle make less concentrated urine
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- **To make diluted urine is somehow easy to understand. The kidneys needs just to actively transport NaCl at the collecting duct and end up with diluted urine=hypo-osmolar urine.**
  - **To make concentrated urine was an enigma for 100 years (Active transport of water is not known). The micropuncture technique came up with the answer.** Using the micropuncture technique scientists measured the osmolarity of inner medullary interstitium and found to be hyperosmolar.
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# Introduction

- Before we start the lecture, we ask the following question: Why we must drink water?
- Normally, we must excrete 700 mOsm/day as a minimum amount (in a complete bed rest individual), or 1000 mOsm/D at normal daily activity.
- The kidney can make a concentrated urine up to 1400 mOsm/l
- Therefore, 0.5 l is the minimum daily obligatory volume of urine (MDOVU):  $(700/1400)$  or 714 ml  $(1000/1400)$  during normal daily activity
- MDOVU is:
  - Infants < 1 ml/kg/h
  - Children < 0.5 ml/kg/h
  - Adults < 0.3 ml/kg/h
- In general  $MDOVU = 300 \text{ ml/m}^2 \text{ BSA/D}$

# Water Balance

	Intake	Output
1.	Metabolism 200 ml	GIT 100 ml
2.	Drinking 1600 ml	Skin 600 ml
3.	Food 700 ml	Respiratory 300 ml
4.		Urine 1500
	2500	2500



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- **In order to form Concentrated Urine, two conditions must be met:**
  - **1. Hyperosmolar interstitium around the medullary collecting ducts**
  - **2. ADH to permit H<sub>2</sub>O permeability.**
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## **How to generate hyperosmolar interstitium?**

By the so called “**single effect**”. In thick ascending loop of Henle,  $\text{Na}^+$ - $\text{K}^+$ - $2\text{Cl}^-$  transporter without  $\text{H}_2\text{O}$  reabsorption, making interstitium hyperosmolar with 700 mOsm/L

- The rest is made by urea
- $\text{Na}^+$  that is reabsorbed must not be removed from the area, and therefore blood flow in Vasa Recta must be low (2% of renal blood flow). High blood flow does not allow this hyperosmolar media to build up.

# ADH

- Both ADH and oxytocin are composed of 9 aa (small peptides)
- ADH: 5/6<sup>th</sup> from supraoptic nuclei and 1/6<sup>th</sup> from paraventricular nuclei.
- ADH → V2 receptor (AQP V2) → cAMP → intracellular vesicles → aquaporins → in luminal side (takes 5-10 min).
- AQP V3 and V4 do not respond to ADH.
- ADH receptors are found in last one third of DT and further.
- **Functions of ADH:**
  - 1. ↑ H<sub>2</sub>O reabsorption from last one third of DT and further.
  - 2. Enhances active NaCl reabsorption from last one third of DT and further.
  - 3. Enhances urea reabsorption from IMCD.
  - The last two factors make medulla hyperosmolar.

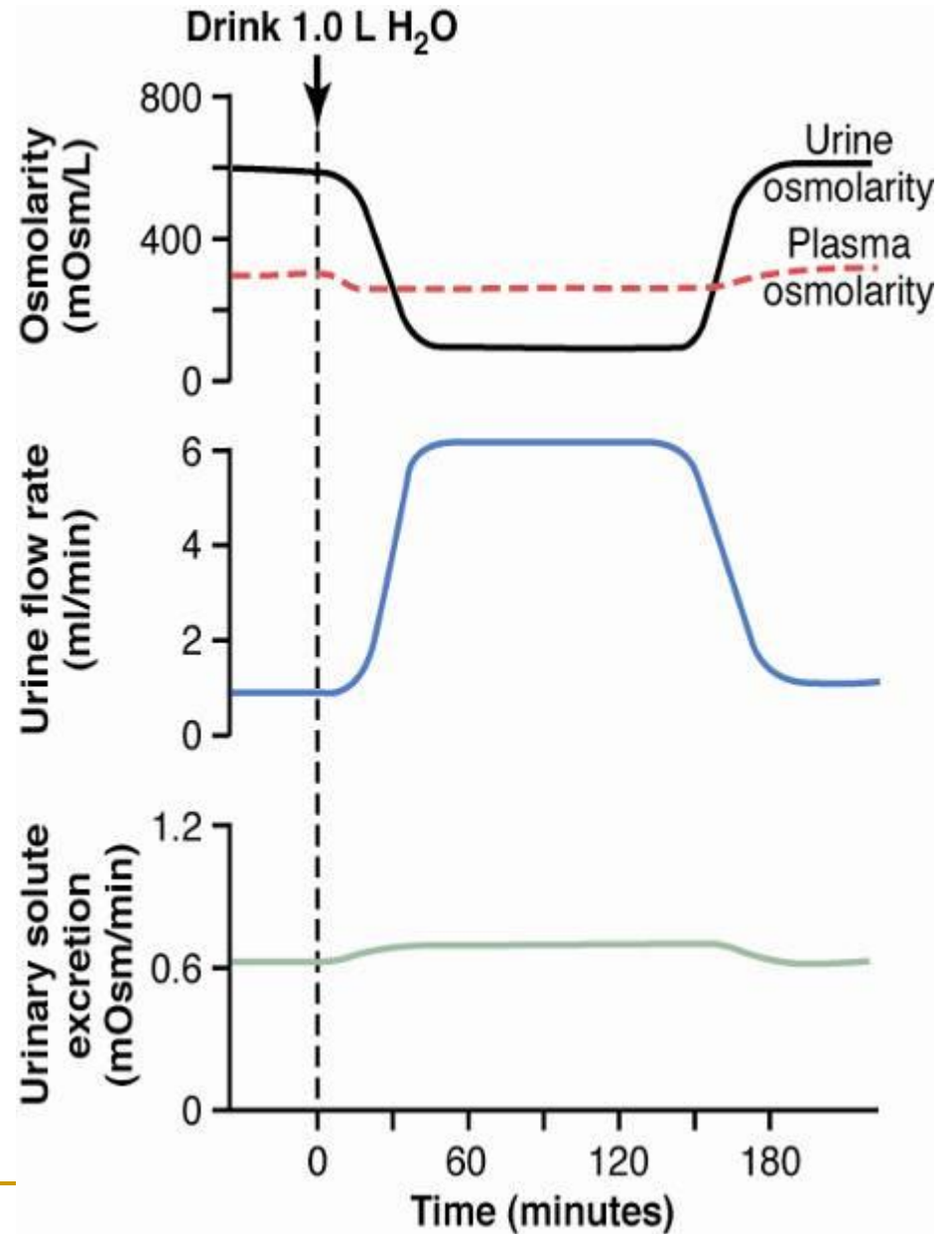
# Control of Extracellular Osmolarity (NaCl Concentration)

- ADH
  - Thirst
- } → ADH -Thirst Osmoreceptor System

## Mechanism:

increased extracellular osmolarity (NaCl)  
stimulates ADH release, which increases  
H<sub>2</sub>O reabsorption, and stimulates thirst  
(intake of water)

# Water diuresis in a human after ingestion of 1 liter of water.

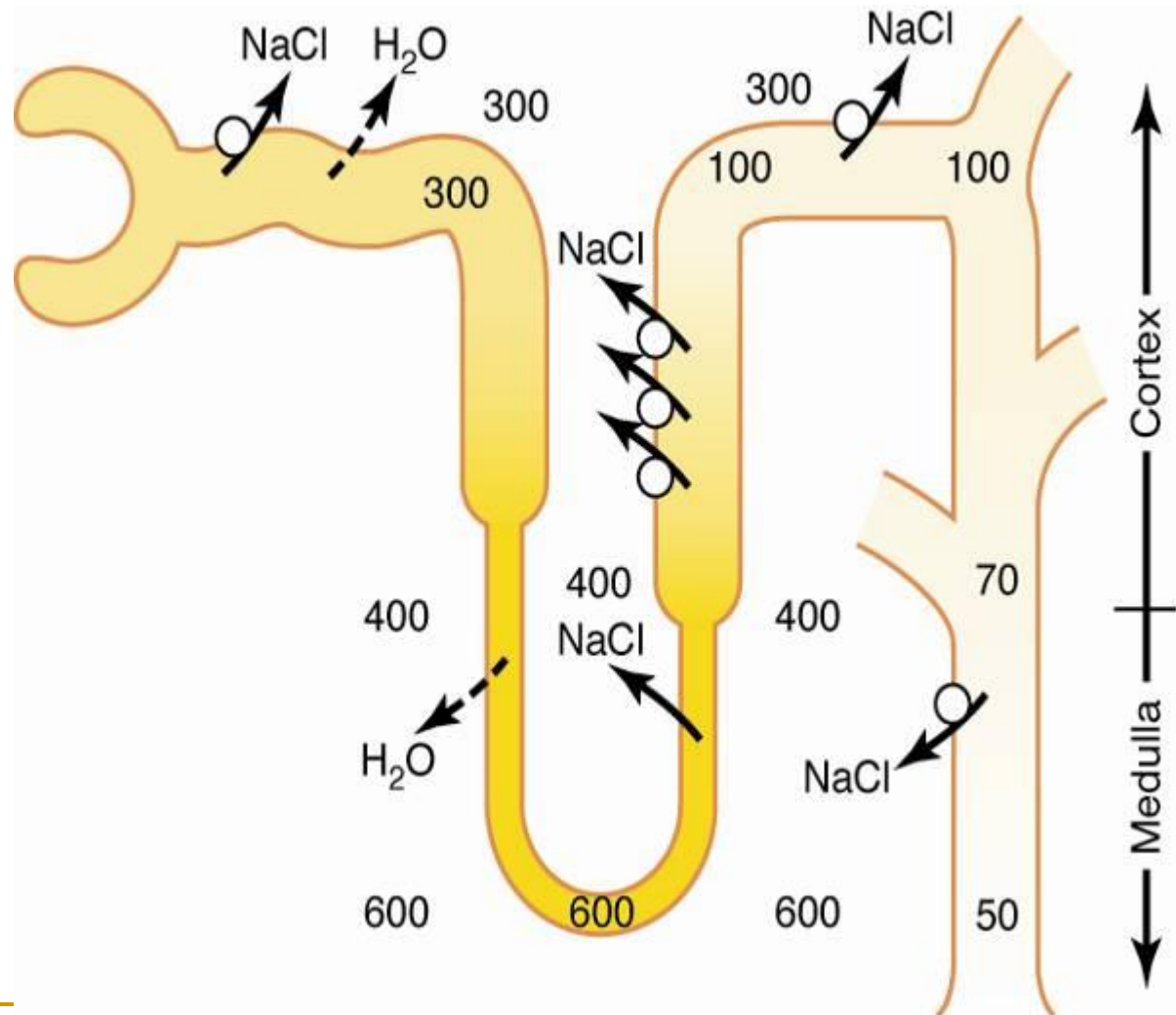


# Formation of a dilute urine

Continue electrolyte reabsorption  
Decrease water reabsorption

## Mechanism:

Decreased ADH release  
and reduced water permeability in distal  
and collecting  
tubules



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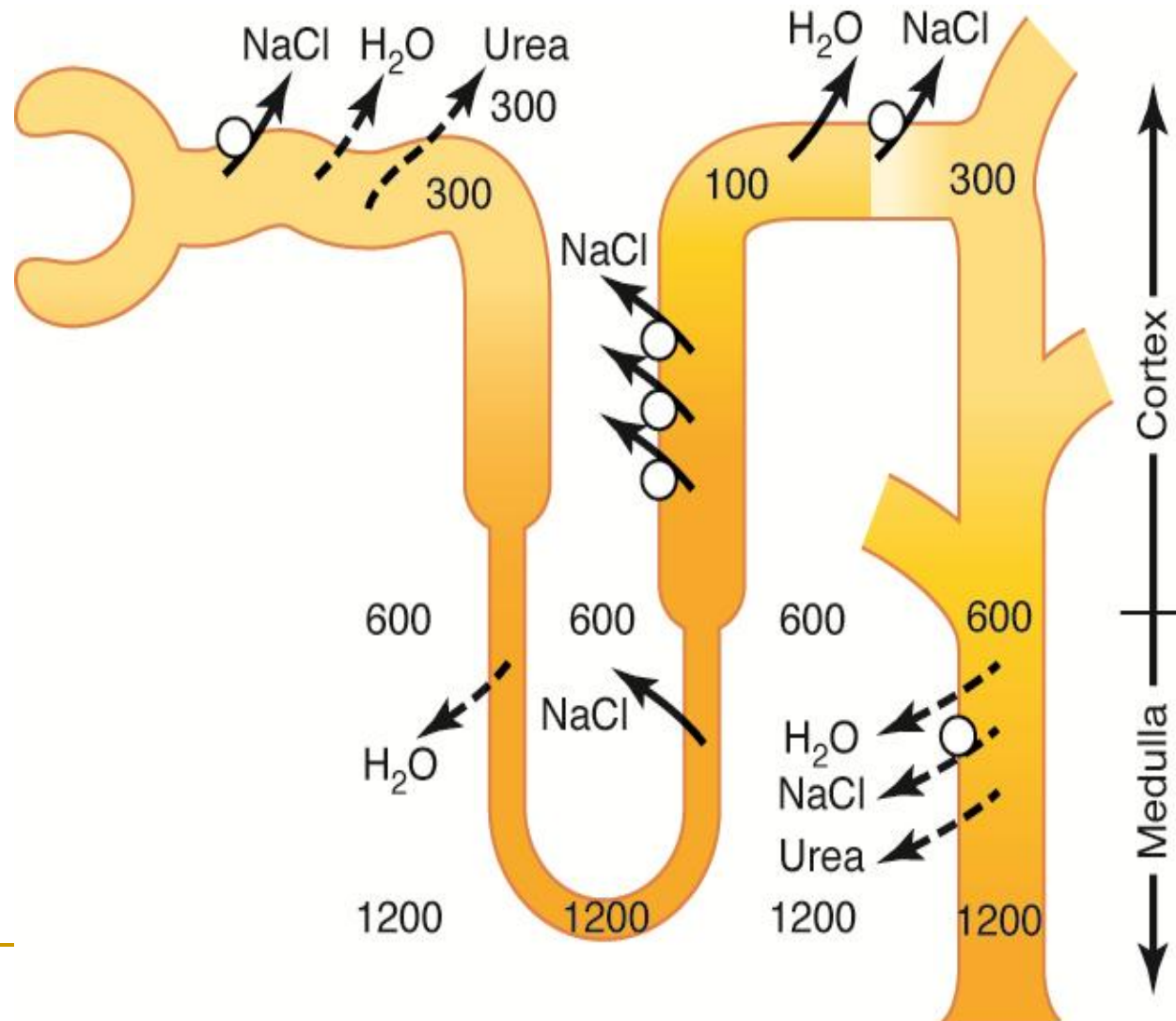
# Formation of a Concentrated Urine

- Continue electrolyte reabsorption
- Increase water reabsorption

## Mechanism :

- Increased ADH release which increases water permeability in distal and collecting tubules
  - High osmolarity of renal medulla
  - Countercurrent flow of tubular fluid
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## Formation of a Concentrated Urine when antidiuretic hormone (ADH) are high.





# Obligatory Urine Volume

Again: The **minimum** urine volume in which the excreted solute can be dissolved and excreted

## Example:

If the max. urine osmolarity is 1400 mOsm/L, and 700 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is:

$$\frac{700 \text{ mOsm/d}}{1400 \text{ mOsm/L}} = 0.5 \text{ L/day}$$

# Obligatory Urine Volume

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,
- If 700 mOsm of solute must be excreted each day to maintain electrolyte balance
- obligatory urine volume = ?

$$\frac{700 \text{ mOsm/d}}{300 \text{ mOsm/L}} = 2.3\text{L/day}$$

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

- Active transport of  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$  and other ions from thick ascending loop of Henle into medullary interstitium
  - Active transport of ions from medullary collecting ducts into interstitium
  - Passive diffusion of urea from medullary collecting ducts into interstitium
  - Diffusion of only small amounts of water into medullary interstitium
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# Summary of Tubule Characteristics

Tubule Segment	Active NaCl Transport	Permeability		
		H <sub>2</sub> O	NaCl	Urea
Proximal	++	+++	+	+
Thin Desc.	0	+++	+	+
Thin Ascen.	0	0	+	+
Thick Ascen.	+++	0	0	0
Distal	+	+ADH	0	0
Cortical Coll.	+	+ADH	0	0
Inner Medullary Coll.	+	+ADH	0	+++

# Countercurrent multiplier system in the loop of Henle.

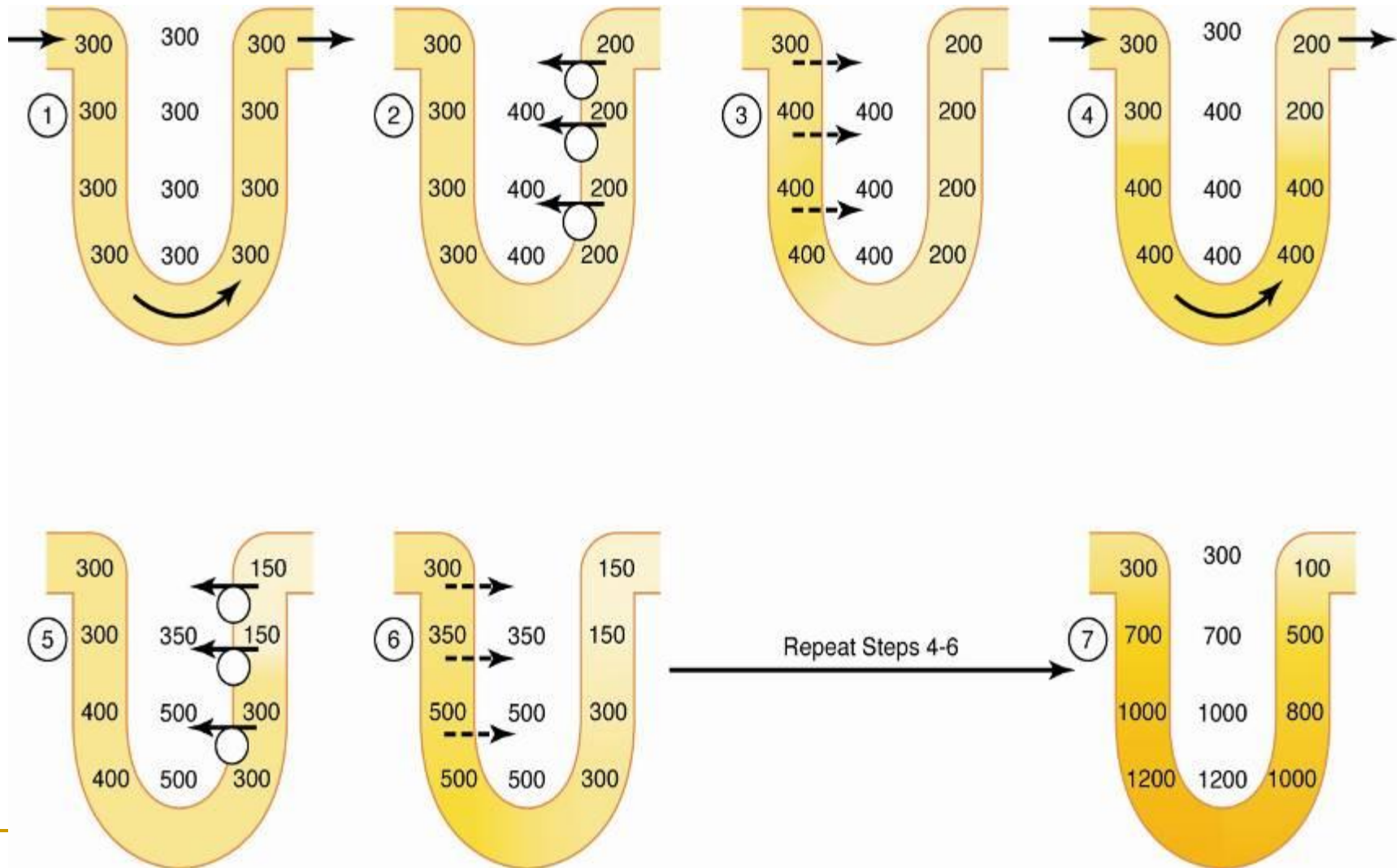
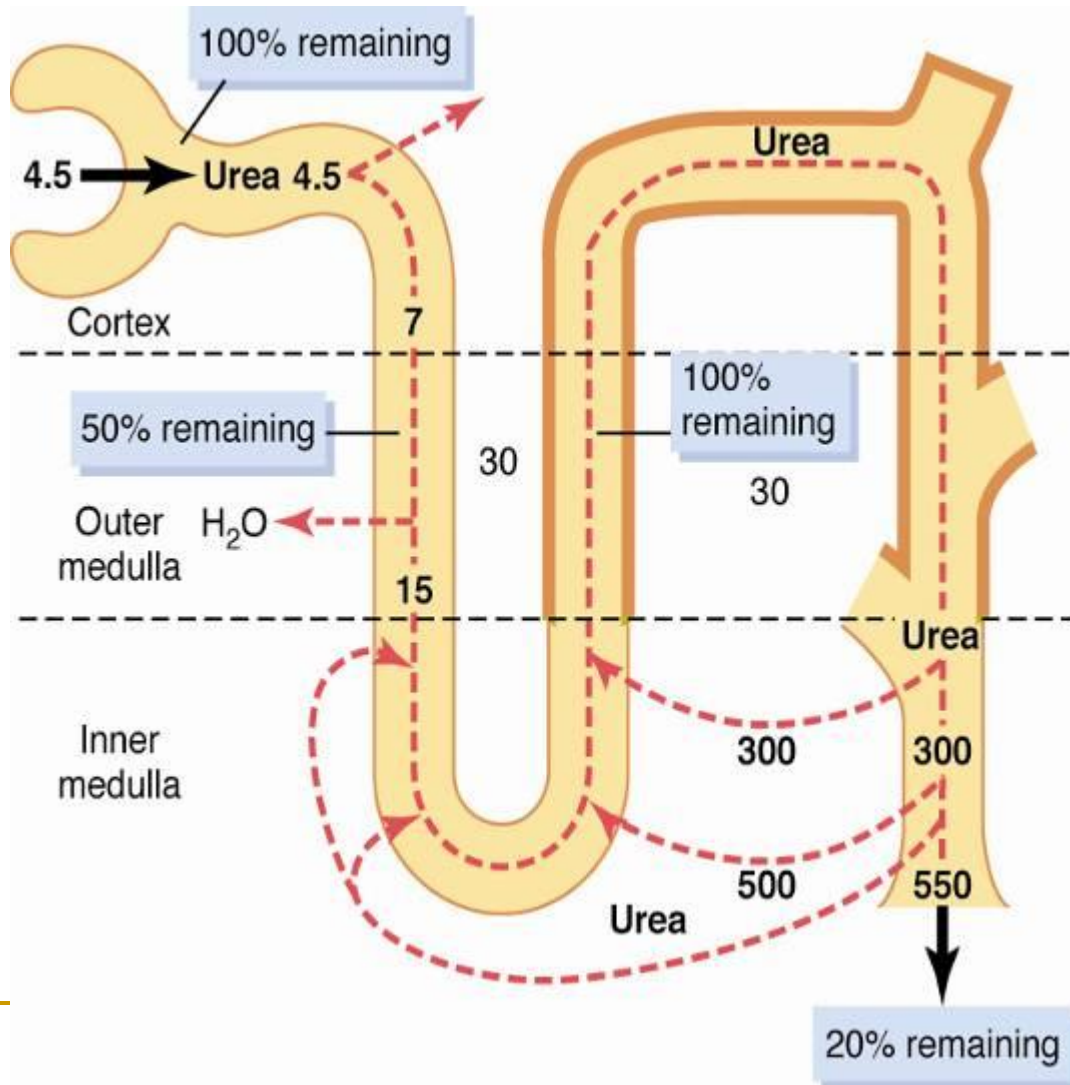


Figure 28-4  
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# Net Effects of Countercurrent Multiplier

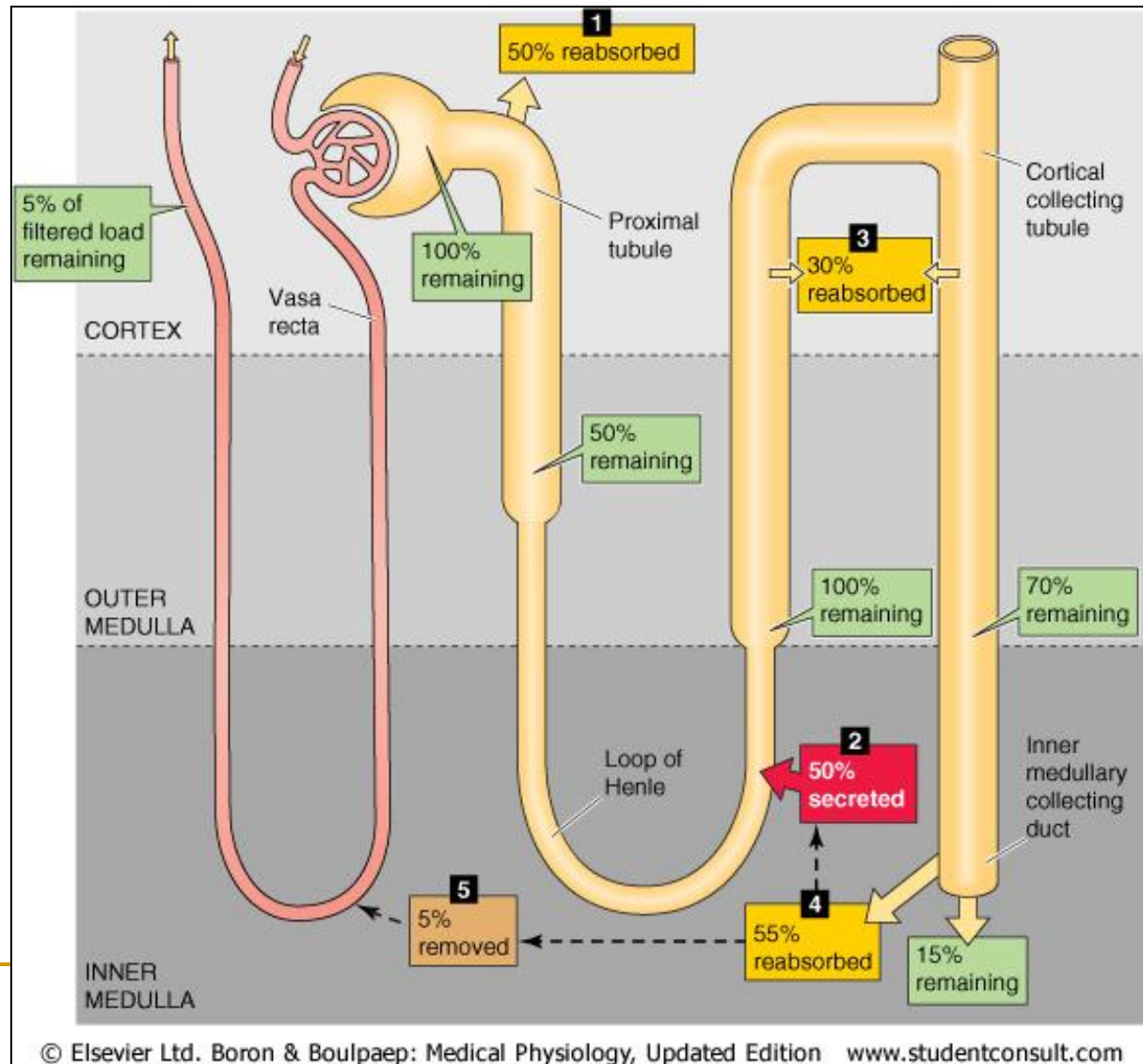
1. More solute than water is added to the renal medulla.  
i.e solutes are “trapped” in the renal medulla
2. Fluid in the ascending loop is diluted
3. Most of the water reabsorption occurs in the cortex  
(i.e. in the proximal tubule and in the distal convoluted tubule) rather than in the medulla
4. 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.



# Urea recycling

- Urea toxic at high levels, but can be useful in small amounts.
- Urea recycling causes buildup of high [urea] in inner medulla.
- This helps create the osmotic gradient at loop of Henle so  $H_2O$  can be reabsorbed.





# Urea Recirculation

- 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

- The vasa recta serve as countercurrent exchangers
- Vasa recta blood flow is low (only 1-2 % of total renal blood flow)

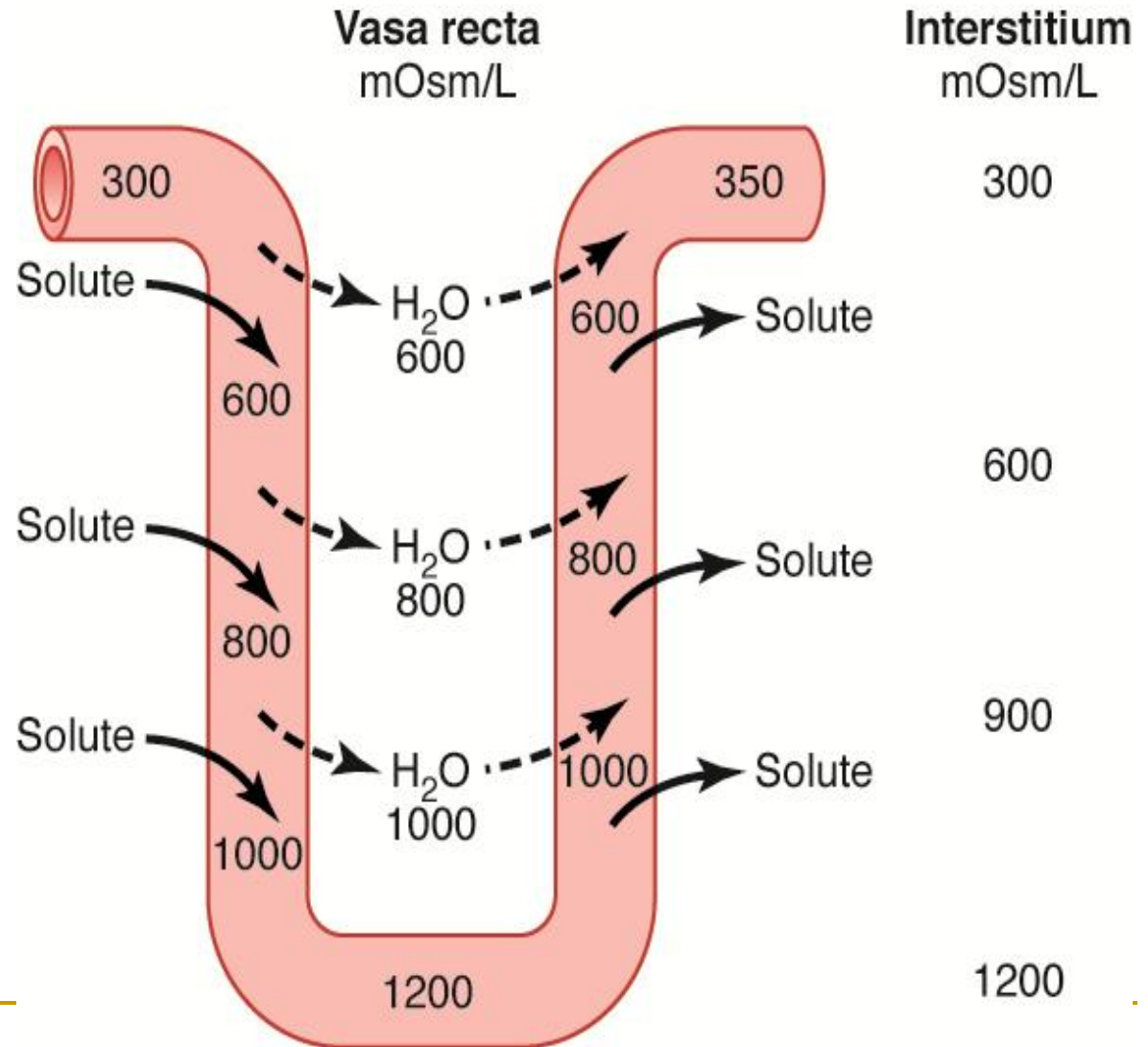


Figure 28-7

# Changes in osmolarity of the tubular fluid

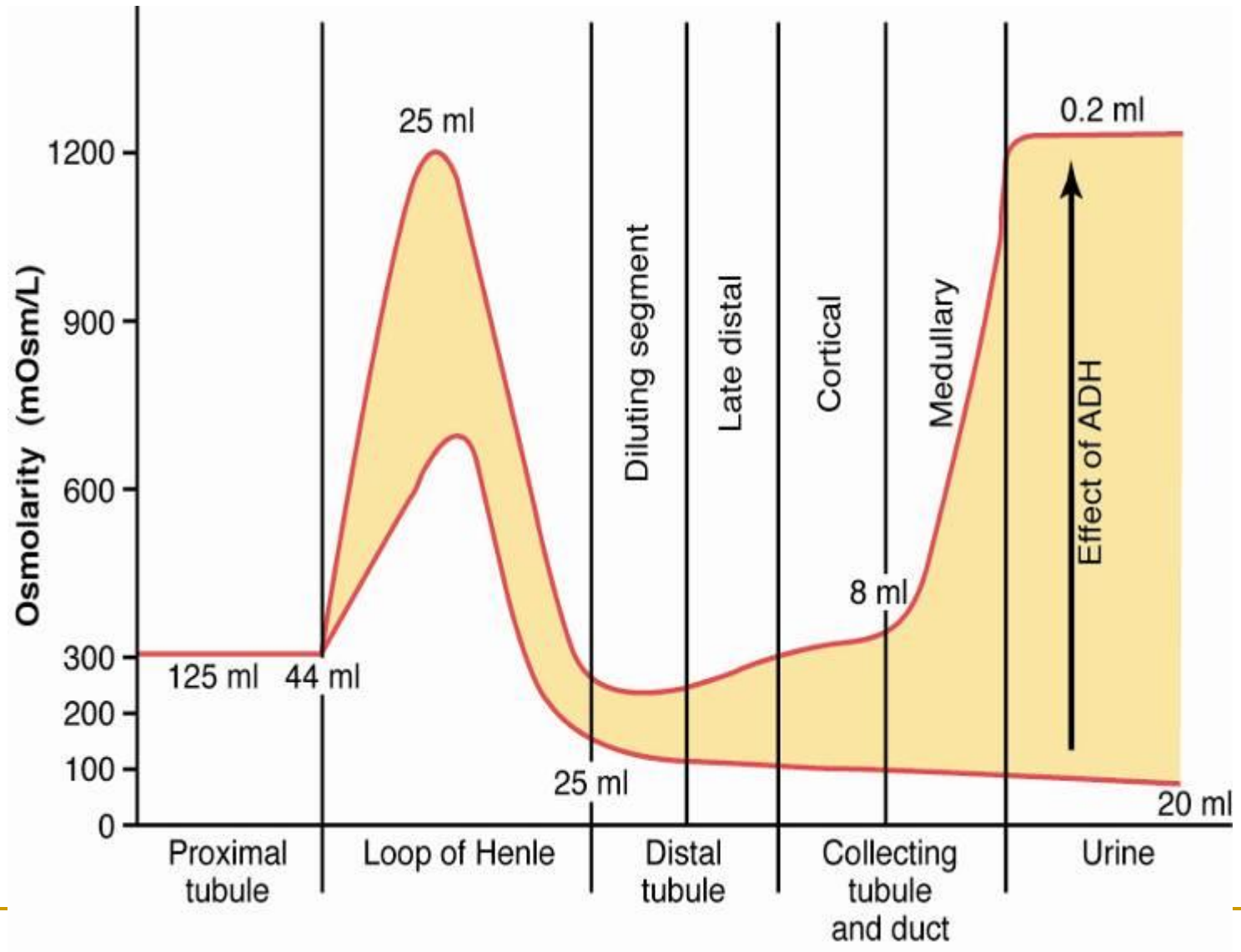


Figure 28-8  
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## **Summary of water reabsorption and osmolarity in different parts of the tubule**

- 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 ( $C_{H_2O}$ ) (rate of solute-free water excretion)

$$C_{H_2O} = V - \frac{U_{osm} \times V}{P_{osm}}$$

where:

$U_{osm}$  = urine osmolarity

$V$  = urine flow rate

$P$  = plasma osmolarity

If:  $U_{osm} < P_{osm}$ ,  $C_{H_2O} = +$

If:  $U_{osm} > P_{osm}$ ,  $C_{H_2O} = -$

# 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 ?



# Answer

$$CH_2O = V - \frac{U_{osm} \times V}{P_{osm}}$$

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

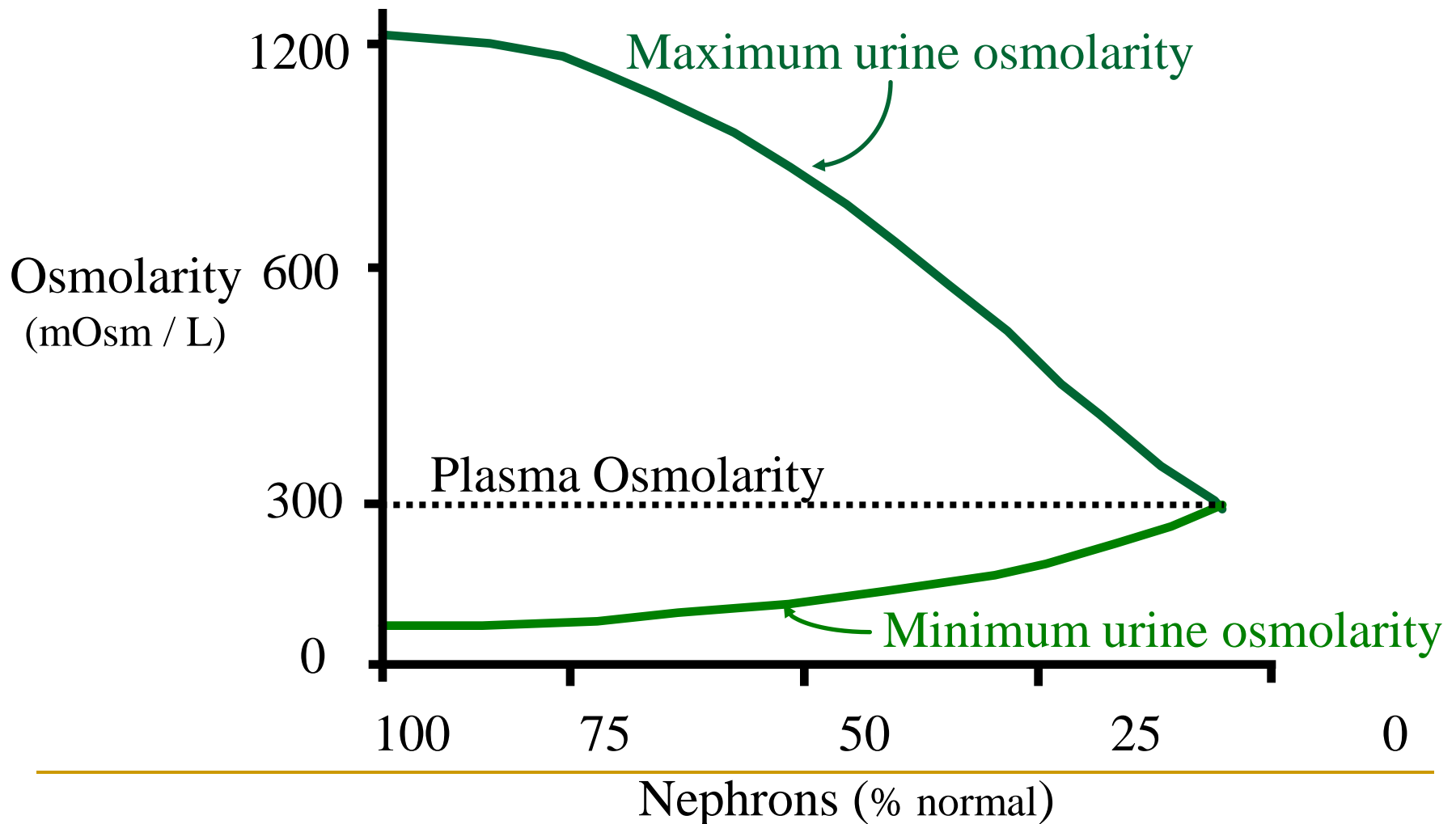
$$= 6.0 - 3.0$$

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

# Disorders of Urine Concentrating Ability

- Failure to produce ADH :  
“Central” diabetes insipidus
- Failure to respond to ADH:  
“nephrogenic” diabetes insipidus
  - impaired loop NaCl reabs. (loop diuretics)
  - drug induced renal damage: lithium, analgesics
  - malnutrition (decreased urea concentration)
  - kidney disease: pyelonephritis, hydronephrosis, chronic renal failure

## Development of Isosthenuria With Nephron Loss in Chronic Renal Failure (inability to concentrate or dilute the urine)



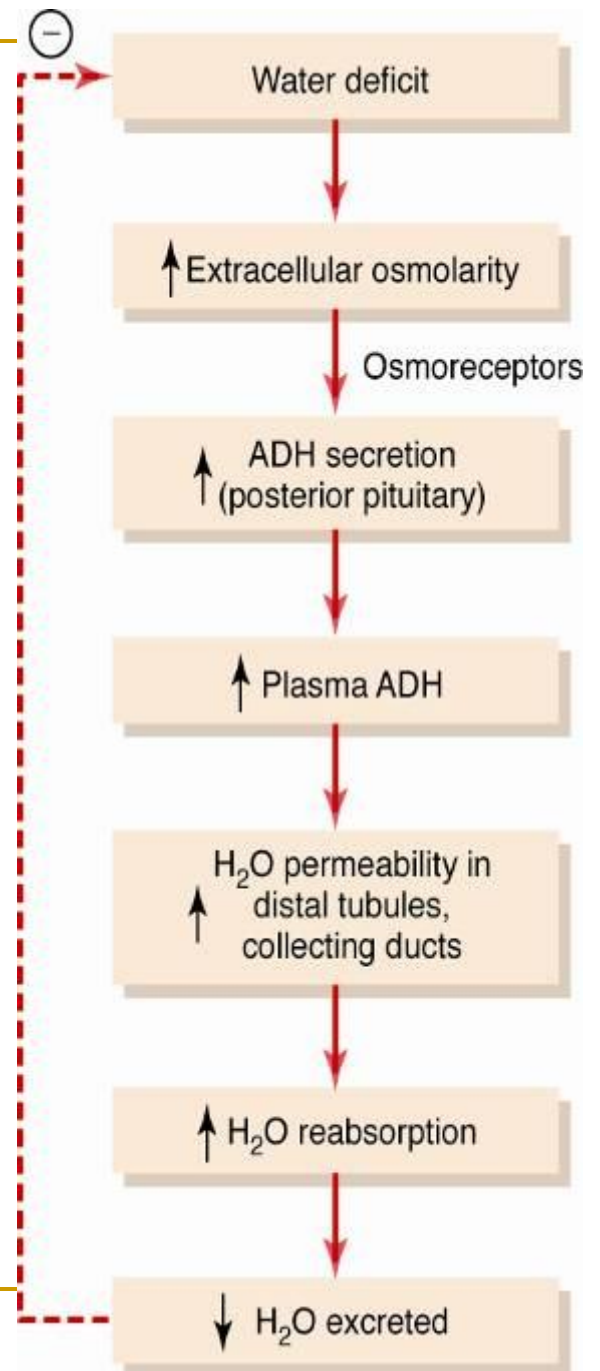
# Total Renal Excretion and Excretion Per Nephron in Renal Failure

Normal

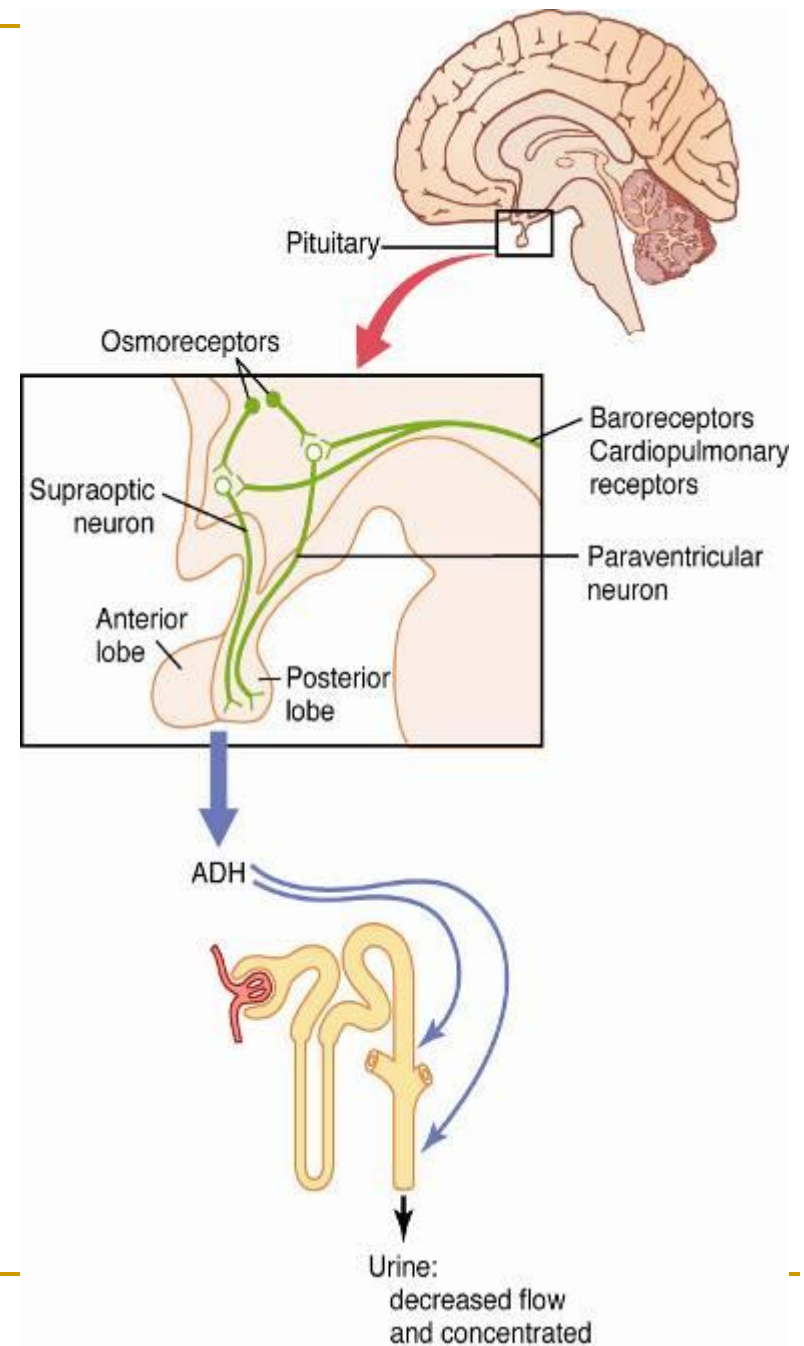
75 % loss of  
nephrons

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.**



ADH synthesis in the magnocellular neurons of hypothalamus, release by the posterior pituitary, and action on the kidneys



# Stimuli for ADH Secretion

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

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## **ADH is released upon:**

1. Increased osmolarity (Osmoreceptors in hypothalamus). An increase of 1% (2-3 mOsm/l) is enough to stimulate ADH secretion.
  2. Decreased blood pressure (arterial baroreceptor reflex (high-pressure regions such as aortic and carotid sinus, and low-pressure regions such as cardiac atria and cardiopulmonary reflexes),
  3. Decreased blood volume. We need a decrease of blood volume by 10% to stimulate ADH release.
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The effect of increased plasma osmolarity or decreased blood volume.

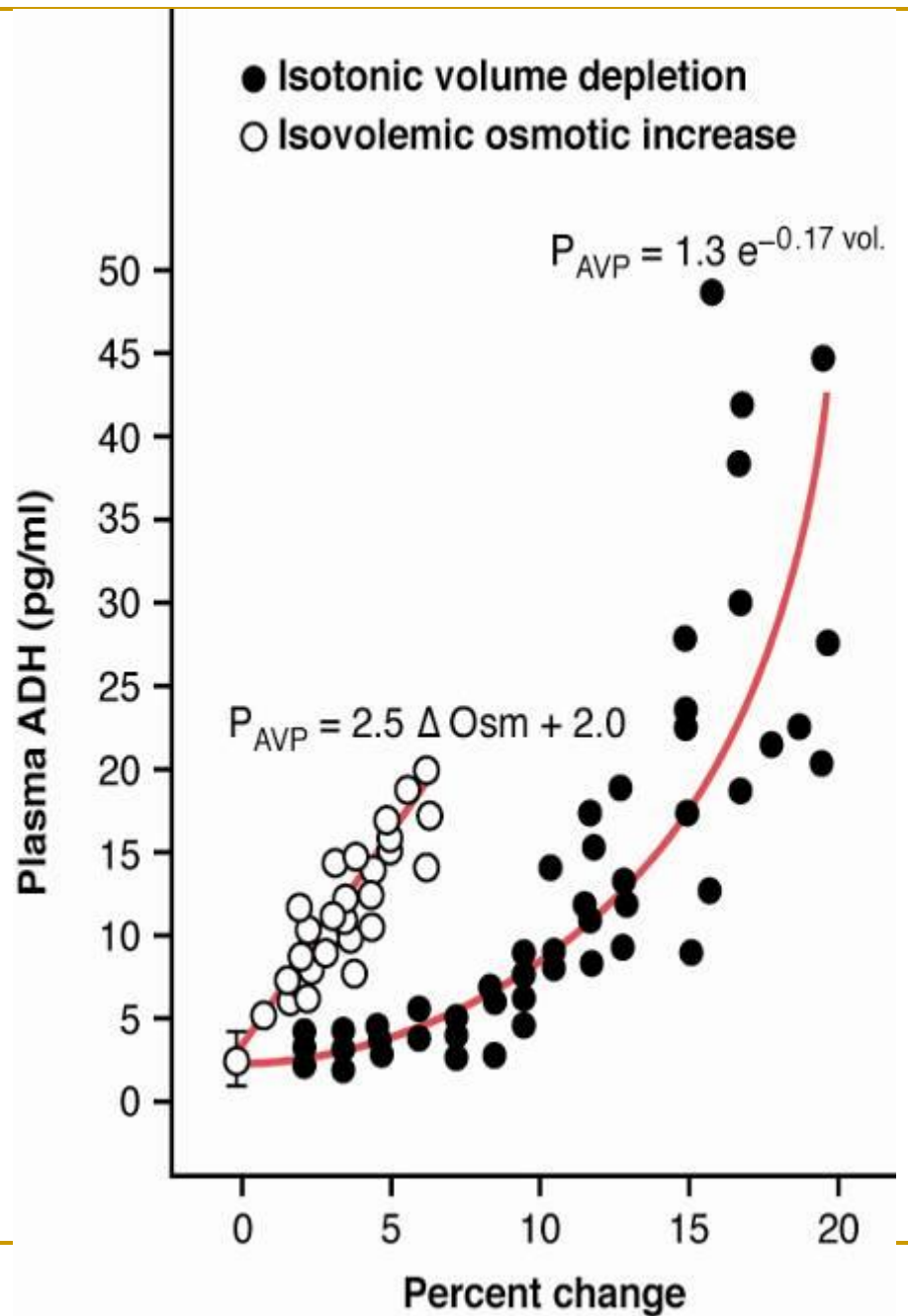


Figure 28-11

# Factors That Decrease ADH Secretion

- Decreased osmolarity
- Increased blood volume (cardiopulmonary reflexes)
- Increased blood pressure (arterial baroreceptors)
- Other factors :
  - alcohol
  - clonidine (antihypertensive drug)
  - haloperidol (antipsychotic, Tourette's)

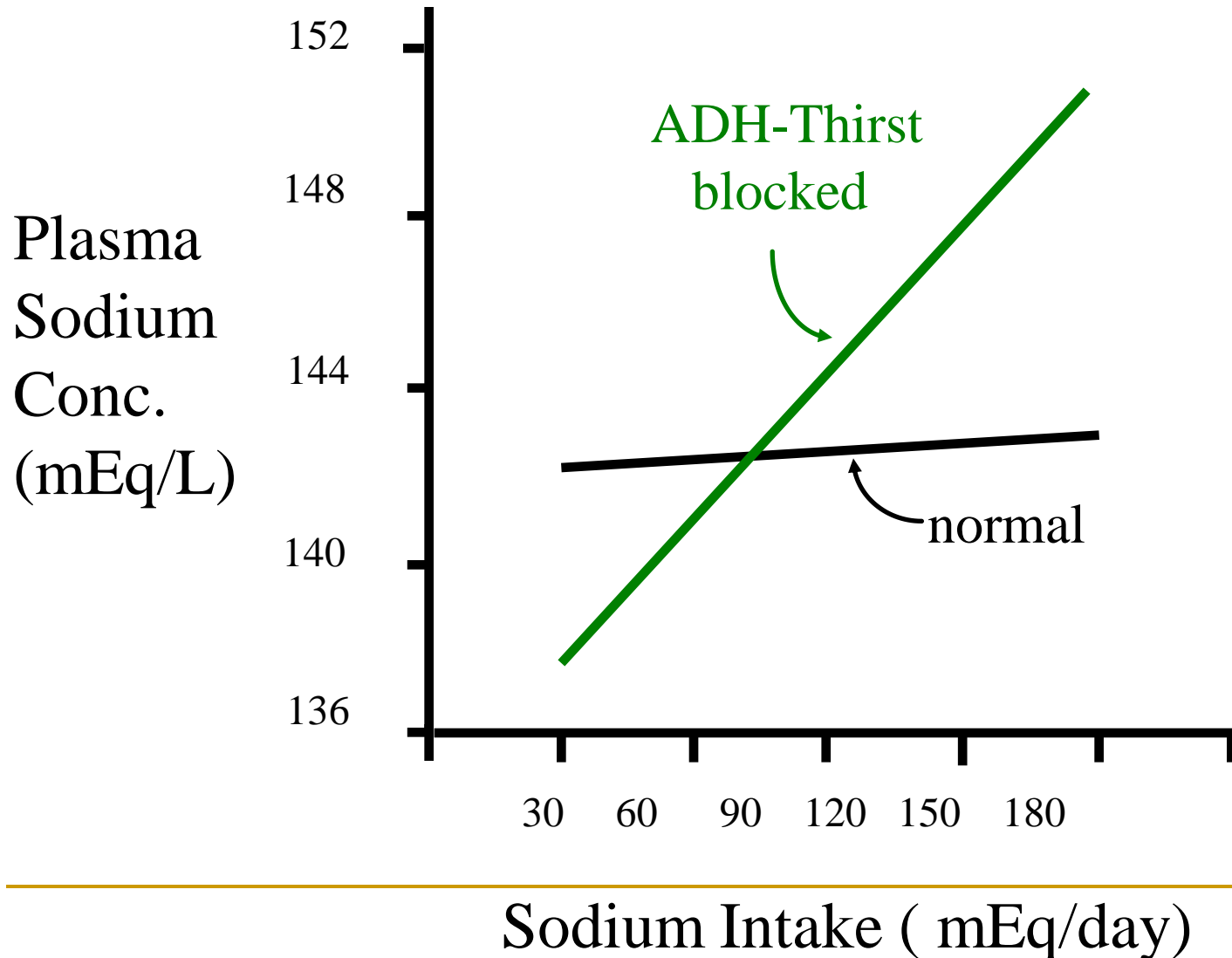
# Stimuli for Thirst

- Increased osmolarity
- Decreased blood volume  
(cardiopulmonary reflexes)
- Decreased blood pressure  
( arterial baroreceptors)
- Increased angiotensin II
- Other stimuli:
  - dryness of mouth

# Factors That Decrease Thirst

- Decreased osmolarity
- Increased blood volume  
(cardiopulmonary reflexes)
- Increased blood pressure  
( arterial baroreceptors)
- Decreased angiotensin II
- Other stimuli:
  - Gastric distention

## Effect of Changes in Sodium Intake on Plasma Sodium After Blocking ADH-Thirst System



# Effect of Changes in Sodium Intake on Plasma Sodium After Blocking Aldosterone or Ang II System

