Concentration and Dilution of Urine 1 and 2
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OBJECTIVES:

After studying this lecture, the student should understand:

1. Responses to water deprivation.
2. Responses to water drinking.
4. How countercurrent multiplication contributes to the creation of a corticopapillary gradient.
5. How urea recycling contributes to the creation of a corticopapillary gradient.
6. The role of countercurrent exchange in vasa recta.
7. The cellular actions of ADH.
8. Mechanisms involved in production of hyposmotic (dilute) urine.
9. How to calculate free water clearance.

I. REGULATION OF BODY FLUID OSMOLARITY

The mechanisms which regulate our body fluid osmolarity are those regulating water reabsorption by the kidney. Most of the filtered water (about 2/3) is reabsorbed isosmotically by the proximal tubule. During passage through the loops of Henle, NaCl is reabsorbed without water. A variable amount of water is reabsorbed by the distal tubules and collecting ducts. The amount of water absorbed in these distal segments is controlled by antidiuretic hormone (ADH). ADH secretion from the posterior pituitary is controlled by the osmolarity of blood, via osmoreceptors in the anterior hypothalamus.
Figure 1. Responses to water deprivation. Circled numbers correspond to the text. ADH, Antidiuretic hormone.
Figure 2. Responses to water drinking. Circled numbers correspond to the text. ADH, Antidiuretic hormone.
When a **subject is deprived of water** (see Figure 1), his plasma osmolarity increases. This stimulates the secretion of ADH from the posterior pituitary gland, which in turn increases the water permeability of the distal tubules and collecting ducts, thereby promoting the reabsorption of water.

Conversely, when an **individual drinks a large volume of water** (see Figure 2), the consequent dilution of plasma leads to inhibition of ADH secretion, causing decreased water permeability of distal tubules and collecting ducts and excretion of the excess water.

Other agents or situations may influence ADH secretion. Alcohol inhibits ADH secretion, causing a water diuresis. An important stimulus for ADH secretion is decreased blood volume (via the "volume receptors" in the left atria); this mechanism allows the body to conserve water in severe hemorrhage.

**II. FORMATION OF HYPEROSMOTIC (CONCENTRATED) URINE**

The ability to form **hyperosmotic urine** is associated with the presence of **Loops of Henle**. Between various species, the longer the loop of Henle, the greater the ability to concentrate the urine. Desert rodents have the longest loops of Henle and the greatest concentrating ability. The role of the loops of Henle is to create a large osmotic gradient from the outermost part of the kidney (cortex) to the innermost part (papilla). This gradient is called the **corticopapillary osmotic gradient**.

We shall consider the following components in the formation of hyperosmotic urine: (1) Establishment of the corticopapillary gradient by the loops of Henle (**countercurrent multiplication**). (2) The **vasa recta** which help maintain the gradient. (3) **ADH**, which makes the distal tubule and collecting duct cells permeable to water, allowing osmotic equilibration of tubular fluid with the hyperosmotic interstitium.
A. Formation of hyperosmotic urine--overview

In the above diagram, the numbers are osmolarity of tubular fluid or interstitial fluid. The heavy outline indicates water impermeable segments of the nephron. The following events occur along the nephron.

1. In proximal tubule, 2/3 of the glomerular filtrate is reabsorbed isosmotically. Fluid entering the loop of Henle has an osmolarity of equal to that of glomerular filtrate, 300 mOsm/L.
2. In thick ascending limb of Henle, the cells are impermeable to water. Here, NaCl is reabsorbed (by Na-K-2Cl cotransport) without water. This process makes the surrounding medullary and papillary interstitial fluid hyperosmotic to systemic plasma; the loops of Henle serve as countercurrent multipliers to create this hyperosmolarity (see below). The fluid which leaves the thick ascending limb is hyposmotic. Because the thick ascending limb reabsorbs NaCl without water and the exiting fluid is hyposmotic, it is called the "diluting segment".
3. The first portion of the distal tubule is also water-impermeable and is called the "cortical diluting segment". It is not part of the loop of Henle, so it does not participate in countercurrent multiplication. It can, however, further dilute the tubular fluid.

4. Circulating ADH levels are high during antidiuresis, making the cells of the late distal tubule and collecting duct permeable to water. Water will flow from low osmolarity (in the tubule lumen) to high osmolarity (surrounding interstitium) until osmotic equilibrium is achieved. The maximum urine osmolarity will be equal to the interstitial osmolarity at the tip of the papilla (about 1200 mOsm/L in humans).

B. Countercurrent multiplication (establishment of the corticopapillary osmotic gradient)

![Figure 4. Mechanism of countercurrent multiplication in a loop of Henle. Circled numbers correspond to the text; numbers are osmolarities of tubular fluid or interstitial fluid; arrows show the direction of fluid flow; heavy outline shows water impermeability of the ascending limb.](image-url)
The osmolarity of the fluid in Henle's loop is shown as a series of discontinuous steps. In the initial state the loop is filled with fluid with osmolarity of 300 mOsm/L. In Step 1, NaCl is reabsorbed without water along the length of the thick ascending limb (called the "single effect") rendering the interstitial fluid hyperosmotic and the thick ascending limb fluid hyposmotic. The thin descending limb is permeable to water and so water leaves the descending limb until its tubular fluid has the same osmolarity as the adjacent interstitial fluid. Now there is a 200 mOsm/L osmotic gradient between descending and ascending limbs. In Step 2, fluid is shifted along the nephron, introducing new 300 mOsm/L fluid into the descending limb and ejecting dilute fluid from the ascending limb. The "single effect" creating a 200 mOsm/L gradient occurs again in Step 3. Continuation of the process will multiply the gradient more, until the fluid at the bend of the loop is 1200 mOsm/L.

C. Role of urea in the corticopapillary gradient

During antidiuresis, about 60% of the solute deposited in the medulla and papilla is NaCl (via countercurrent multiplication). The remaining 40% is urea. Deposition of urea in the medulla and papilla is aided by "urea recycling" which diverts some urea from medullary collecting duct fluid back into the loops of Henle. Urea reabsorption from collecting ducts is high during antidiuresis in part because of differential effects of ADH on urea and water permeabilities in the terminal nephron segments. They are:

1. ADH increases H₂O permeability in the late distal tubule, outer and inner medullary collecting ducts.
2. ADH increases urea permeability in the inner medullary collecting ducts, but not in the late distal or outer medullary collecting ducts.

The consequences of this differential permeability effect are shown in the following figure.
ADH increases the water, but not urea, permeability of the late distal tubule and outer medullary collecting duct; water is reabsorbed, but urea is not. Consequently, the urea concentration of the collecting duct fluid increases. In the inner medullary collecting ducts, the urea concentration has become very high. Here, ADH does increase the urea permeability, so urea diffuses out of the tubular fluid, down this steep concentration gradient, into the surrounding interstitium. Thus, it becomes a major solute in the inner medulla and papilla.

D. **Countercurrent exchange in vasa recta**

The vasa recta are the capillaries which supply the medulla and papilla of the kidney with oxygen and nutrients necessary for active transport. They also remove the water reabsorbed by the descending limbs of Henle and the collecting ducts. If blood flow to these regions was very high, the solutes accumulated by countercurrent multiplication and urea recycling would be washed away. Dissipation of the corticopapillary gradient is prevented because (1) **blood flow through this region is low** and (2) **the vasa recta act as countercurrent exchangers**. The figure below illustrates the principle of countercurrent exchange in vasa recta.
Countercurrent exchange is **entirely passive**. Blood enters the vasa recta with an osmolarity of 300 mOsm/L. In the descending limb, water diffuses out and solute diffuses in, increasing the osmolarity of the vasa recta blood until it equals that of the adjacent interstitium. In the ascending limb, the reverse occurs, with solutes diffusing out and water diffusing in, decreasing the osmolarity of the blood. Thus, the vasa recta blood is in osmotic equilibrium with the interstitium and helps maintain the corticopapillary osmotic gradient.

Note that the blood leaving the vasa recta has an osmolarity of 325 mOsm/L. Thus, there is some depletion of medullary solutes; these will be replaced by the ongoing processes of countercurrent multiplication and urea deposition.

**E. Cellular actions of ADH**

\( V_2 \) receptors for ADH are found in **basolateral membranes** of principal cells in late distal tubule and collecting duct. When ADH binds to its receptor, adenylylate cyclase (which is coupled to the receptor by a G\(_s\) protein), is activated; adenylylate cyclase catalyzes the conversion of ATP to cyclic AMP. Cyclic AMP, in turn activates protein kinase(s) which phosphorylates proteins in or near the luminal membrane. The ultimate
physiologic action of ADH is the insertion of "water channels" (aquaporin2, or AQP2) in the luminal membrane, making the cells permeable to water; this occurs within minutes of hormone binding to peritubular receptors.

III. FORMATION OF HYPSOMOTIC (DILUTE) URINE

Urine can be dilute with respect to blood (<300 mOsm/L). E.g., following ingestion of a large volume of water, ADH secretion is suppressed, water is not reabsorbed by the collecting ducts, and the urine is dilute. In diabetes insipidus, where there is absence of ADH (central diabetes insipidus) or resistance of the principal cells to ADH (nephrogenic diabetes insipidus), large volumes of dilute urine are excreted.
Again, the numbers are osmolarity and the heavy outline shows water impermeability. Note the following important differences from the schematic nephron which was making hyperosmotic urine.

A. ADH is very low or absent.
B. The osmolarity of the medullary and papillary interstitium is only about 1/2 that of the concentrating kidney (600 vs. 1200 mOsm/L). There are two major reasons: ADH increases the activity of the Na-K-2Cl cotransporter in the thick ascending limb. When ADH is low or absent, this important step in the countercurrent multiplication is reduced. Note that the osmolarity of the fluid leaving the thick ascending limb is slightly elevated (120 rather than 100), because less NaCl has been reabsorbed without water. Second, less urea is deposited in the medulla and papilla because the lack of ADH stops urea recycling.
C. The entire distal tubule and collecting duct is impermeable to water, so there is no osmotic equilibration between tubular fluid and adjacent interstitial fluid. No water is reabsorbed in these segments. In fact, the tubular fluid becomes even more dilute than that leaving the thick
ascending limb, since the distal tubule and collecting ducts reabsorb some NaCl, but no water. The final urine osmolarity can be as low as 75 mOsm/L, with volumes up to 15 L/day (8% of the GFR).

IV. FREE WATER CLEARANCE

"Free water clearance" ($C_{H2O}$), is the amount of water which must be subtracted from or added to urine to make it isosmotic with plasma.

"Free water" is water that is devoid of solute, or solute-free water. It is “produced” in the diluting segments of the nephron (thick ascending limb and early distal tubule) where NaCl is absorbed without water; the water that is left behind is solute-free water. **If ADH is low**, the "free water" produced in the diluting segments will be excreted ("positive free water"); relative to plasma, the urine will be hyposmotic. **If ADH is high**, all the free water produced in the diluting segments (plus more) will be reabsorbed by collecting ducts and no free water will be excreted ("negative free water"); relative to plasma, the urine will be hyperosmotic.

\[
C_{H2O} = V - C_{osm}
\]

where:
- $V$ = urine flow rate
- $C_{osm} = \frac{Uosm \times V}{Posm}$

*(Note! $C_{H2O}$ is not a classical renal clearance.)*

Examples:

1. **If urine is isosmotic to plasma, $C_{H2O}$ is zero:**

   \[
   \begin{align*}
   Posm & = 300 \text{ mOsm/L} \\
   Uosm & = 300 \text{ mosm/L} \\
   V & = 2 \text{ ml/min} \\
   \end{align*}
   \]

   \[
   \begin{align*}
   C_{H2O} & = 2 \text{ ml/min} - \frac{300 \text{ mosm/L}}{300 \text{ mosm/L}} \times 2 \text{ ml/min} \\
   & = 0 \text{ ml/min}
   \end{align*}
   \]

2. **If urine is hyposmotic to plasma, $C_{H2O}$ is positive.** A positive free water clearance would be measured during water diuresis and reflects the function of the diluting segments of the nephron.
Posm = 300 mOsm/L
** Uosm = 1000 mOsm/L
V = 10 ml/min

\[ C_{H2O} = \frac{10 \text{ ml/min}}{\text{ml/min}} - \frac{100 \text{ mosm/L}}{300 \text{ mosm/L}} \times 10 \]
\[ = +6.7 \text{ ml/min} \]

3. **If urine is hyperosmotic to plasma, \( C_{H2O} \) is negative.** A negative free water clearance would be measured during antidiuresis and reflects the concentrating function of the kidney (the cortico-papillary gradient and water reabsorption from collecting ducts).

\[ Posm = 300 \text{ mOsm/L} \]
\[ ** Uosm = 1000 \text{ mOsm/L} \]
\[ V = 0.5 \text{ ml/min} \]

\[ C_{H2O} = \frac{0.5 \text{ ml/min}}{\text{ml/min}} - \frac{1000 \text{ mosm/L}}{300 \text{ mosm/L}} \times 0.5 \text{ ml/min} \]
\[ = -1.2 \text{ ml/min} \]

(Negative free water clearance was thought to be awkward, so the term "free water reabsorption" \( T_{H2O}^c \) was created:

\[ T_{H2O}^c = - C_{H2O} \]

V. **CLINICAL EXAMPLES**

A. **Central Diabetes Insipidus**

**Description.** An 18 year old college freshman suffered a basal skull fracture during an intramural "flag" football game. Shortly thereafter, he developed severe polyuria with a urine output of 15 L/day and severe thirst. He reported the need to drink almost constantly. He was unable to sleep for more than 30 minutes at a time. A blood sample revealed a serum osmolality of 330 mOsm/L, a serum [Na] of 154 mEq/L and a urine osmolality of 90 mOsm/L. During a water restriction test, his urine osmolality remained below 100 mOsm/L. Administration of vasopressin subcutaneously resulted in a prompt increase in urine osmolality to 600 mOsm/L.
**Explanation.** The diagnosis is central diabetes insipidus subsequent to the head injury which damaged the posterior pituitary gland. In this patient, ADH is not being secreted, even though there is a strong osmotic stimulus (plasma osmolarity of 330 mOsm/L). His severe thirst is result of the high plasma osmolarity. The water deprivation test suggests that ADH is absent or is ineffective on the renal collecting tubule. Administration of exogenous ADH caused a prompt increase in water reabsorption, raising the urine osmolarity; this finding confirmed that the defect is in the patient's own pituitary, rather than in the response of the collecting tubule. Lack of pituitary ADH has caused excessive excretion of large volumes of dilute, solute-free urine, raising the plasma osmolarity and [Na].

The treatment would be administration of a long-acting vasopressin analogue (dDAVP) by nasal spray. This ADH analogue has antidiuretic activity but virtually no vasopressor activity and does not induce antibody production, an important feature of long-term therapy.

An interesting response to chronic dehydration (such as in central diabetes insipidus) occurs in the brain. The brain starts to synthesize osmotically active solutes such as sorbitol, which are called osmolytes. These osmolytes stay in the brain cells. Brain ICF osmolarity is increased by these osmolytes to match the increased ECF osmolarity. In the rest of the body cells, water shifts from ICF to ECF (to make ICF/ECF osmolarities equal in steady state), but in the brain, no water shift occurs because the osmolarites are already matched and equal; this response prevents brain cells from shrinking in chronic dehydration.

**B. Nephrogenic Diabetes Insipidus**

**Description.** A male patient receiving lithium therapy for manic-depressive psychosis reports severe and constant thirst and polyuria. Recently, he has not been able to complete his 45 minute drive to work without making a "pit-stop". In his physician's office, a urine sample had an osmolarity of 100 mOsm/l and a serum sample had an osmolarity of 308 mOsm/L and a [Na] of 152 mEq/L. There was no glucose in his urine. His urine osmolarity remained at 100 mOsm/L during a water restriction test and during administration of ADH.

**Explanation.** Diuresis due to diabetes mellitus is excluded by the lack of glucose in the urine. Primary polydipsia is excluded because the serum osmolarity and [Na] are too high rather than too low as would be seen if the primary problem was drinking too much water. The severe polyuria and very low urine osmolarity in the face of an elevated serum osmolarity points to a defect in the concentrating ability of the kidney. (Increased serum osmolarity should, via osmoreceptors, cause increased secretion of
ADH, increased water reabsorption from collecting ducts, resulting in small volumes of concentrated urine. The fact that the urine is dilute shows that the "diluting segment" of the loop of Henle is functioning and therefore the cortico-papillary gradient is probably intact. Thus, the defect must be in ADH, either decreased secretion of pituitary ADH (Central Diabetes Insipidus) or decreased responsiveness of the collecting duct to ADH (Nephrogenic Diabetes Insipidus). The water deprivation test confirms a problem with ADH, but does not distinguish between the two diseases. Since injection of exogenous ADH did not raise urine osmolarity, then the conclusion must be that his collecting ducts do not respond to ADH. Endogenous ADH levels would actually be elevated in this patient due to the strong osmotic stimulus.

Lithium treatment has caused the nephrogenic diabetes insipidus because it interferes with the ability of ADH to generate cAMP in the collecting tubule cells, possibly by inhibiting the stimulatory G protein ($G_s$) of the adenylate cyclase).

Treatment would include stopping the lithium therapy. Thiazide diuretics may be useful as they inhibit NaCl reabsorption in the "cortical diluting segment", thus inhibiting dilution of the urine, and bringing the urine towards isotonicity.

C. Syndrome of Inappropriate ADH (SIADH)

**Description.** A patient with oat-cell carcinoma of the lung is admitted to the hospital after he has a grand mal seizure at home. Laboratory studies yielded the following information:

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Plasma [Na]</td>
<td>110 mEq/L</td>
</tr>
<tr>
<td>Plasma osmolarity</td>
<td>225 mosm/L</td>
</tr>
<tr>
<td>Urine osmolarity</td>
<td>650 mOsm/L</td>
</tr>
</tbody>
</table>

He had a normal blood pressure, both standing up and lying down.

**Explanation.** The plasma [Na] and osmolarity are extremely low. The appropriate response to this low plasma osmolarity would be to turn off ADH secretion which would, in turn cause decreased water reabsorption from collecting ducts, increased urine volume and decreased urine osmolarity. Yet, the patient's kidneys are producing concentrated urine (650 mOsm/L). Thus, the response of the kidney is "inappropriate" for the low plasma osmolarity. The patient has Syndrome of Inappropriate ADH (SIADH) where ADH is secreted when it should be suppressed. Hypovolemia can, via volume receptors, cause increased ADH secretion when there is no osmotic stimulus; however, in this patient there is no evidence of decreased circulating blood volume since the blood pressure is
normal. Rather, ADH is coming from an ectopic source, the oat cell carcinoma. The seizure was due to swelling of the brain within the skull; severe dilution of the ECF caused water to move from extracellular to intracellular fluid, increasing the volume of the brain cells.

The real danger is swelling of the brain, so hypertonic NaCl would be administered acutely to raise the osmolarity of ECF and bring water out of the brain cells. Chronically, the therapy is water restriction.

VI. PRACTICE QUESTIONS

1. A patient visits his physician complaining of frequent voiding and constant thirst. Fasting serum and urine values are given with normal values in ( ).

<table>
<thead>
<tr>
<th></th>
<th>Serum</th>
<th>Urine</th>
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</thead>
<tbody>
<tr>
<td>Sodium, mEq/L</td>
<td>148 (140)</td>
<td>10 (20-80)</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>90 (70-100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Osmolarity, mOsm/L</td>
<td>308 (290)</td>
<td>65 (50-1000)</td>
</tr>
</tbody>
</table>

The most likely cause of the patient's complaints is:

A. diabetes mellitus
B. excessive water drinking
C. hypoaldosteronism
D. lack of ADH
E. syndrome of inappropriate ADH (SIADH)

2. A patient has a urine osmolarity of 100 mOsm/L and a serum osmolarity of 310 mOsm/L. Which test would best distinguish between central diabetes insipidus and nephrogenic diabetes insipidus in this patient?

A. injection of ADH
B. injection of hypertonic saline
C. injection of insulin
D. water deprivation
E. water loading

3. A subject receives an injection of ADH which causes his urine osmolarity to increase from 200 to 600 mOsm/L. Accompanying this rise in urine osmolarity, one would also expect an increase in:

A. serum osmolarity
B. serum Na concentration
C. positive free water clearance (C\textsubscript{H\textsubscript{2}O})
D. urine volume
E. water reabsorption from collecting ducts.

4. Given the following values, what is the free water clearance \( (C_{\text{H}2\text{O}}) \)?
   \[ \text{Posm} = 300 \text{ mOsm/L}; \text{Uosm} = 100 \text{ mOsm/L}; \text{V} = 9 \text{ mL/min} \]

5. Ingestion of 2 liters of distilled water will result in which of the following changes?
   
   A. Increased circulating ADH.
   B. Decreased TF/P osmolarity of proximal tubule fluid.
   C. Increased recycling of urea from medullary collecting ducts into loops of Henle.
   D. Decreased water permeability of collecting ducts.

6. Compare the responses to water deprivation (dehydration) and water drinking with respect to ADH levels, urine osmolarity, and urine volume.

7. What two major processes are responsible for establishing the corticopapillary gradient?

8. What is the expected effect of low ADH (e.g. due to central diabetes insipidus) on the corticopapillary gradient?

9. How do the vasa recta participate in the concentrating mechanism?

10. What is required for production of hyperosmotic urine?

11. What is required for production of hyposmotic urine?

12. Why is serum osmolarity lower than normal in SIADH?

13. Why is serum osmolarity higher than normal in central diabetes insipidus?

**ANSWERS**

1. **Diabetes mellitus** could cause the frequent voiding and thirst, but is ruled out by absence of glucose in urine. **Excessive (primary) water drinking** would cause serum osmolarity and Na to decrease and subsequently the urine osmolarity to decrease; although the urine is quite dilute, the plasma osmolarity is elevated. **Hypoaldosteronism** would cause decreased Na reabsorption by the distal tubule and consequently a high urine Na concentration; instead, the urine Na is actually low in spite of an elevated serum Na. **Lack of ADH** would cause the distal tubules and collecting ducts to reabsorb less water, thus producing large volumes of a dilute urine and as a consequence, raising the serum osmolarity and the serum Na and causing thirst (the correct answer). **SIADH** is ruled out because there would be inappropriately high levels of ADH, causing the collecting ducts to
reabsorb too much water, an inappropriately high urine osmolarity with low urine volume, and as a result a low serum osmolarity. **The answer is D.**

2. The serum and urine osmolarity are consistent with either type of diabetes insipidus. **Injection of exogenous ADH** would cause the collecting tubules to reabsorb more water in the patient with central DI, but not in the unresponsive collecting ducts of the patient with nephrogenic DI; thus in central DI, the urine osmolarity would increase and the plasma osmolarity would decrease; in nephrogenic DI, these would be unaffected and thus we have different responses and a distinguishing test. **Injection of hypertonic saline or water deprivation** would not distinguish because this test would not bypass the role of the patient's own pituitary. **Insulin and water loading** are nonsense answers. **The answer is A.**

3. **The answer is E.** Injection of ADH would, as a result of this action on the collecting ducts, cause a decrease in serum osmolarity, serum Na, and urine volume so A, B, and D are clearly wrong answers. ADH injection would also cause a decrease in positive free water clearance or (an increase in free water reabsorption); free water is generated in the diluting segments (thick asc. limb and early distal tubule) and, in the presence of ADH, reabsorbed in collecting ducts and thus not excreted.

4. 

$$C_{H2O} = V - C_{\text{osm}} = \frac{9 \text{ ml/min} - 100 \text{ mOsm/L} \times 9 \text{ ml/min}}{300 \text{ mOsm/L}}$$

$$= \frac{9 \text{ ml/min} - 3 \text{ ml/min}}{3 \text{ ml/min}}$$

$$= +6 \text{ ml/min} \text{ (a positive } C_{H2O})$$

5. **The answer is D**

A. Increased circulating ADH. (No. ADH secretion would be turned off by dilution of serum osmolarity.)

B. Decreased TF/P osmolarity of proximal tubule fluid. (No. Proximal water reabsorption and TF/P osmolarity are unaffected by any of the mechanisms involved in concentrating and diluting urine. It's always 1.0.)

C. Increased recycling of urea from medullary collecting ducts into loops of Henle. (No. Urea recycling is increased by increased ADH due to the differential sensitivity of cortical and medullary collecting duct urea permeability. In this case, ADH is turned off by drinking water and so urea recycling would be decreased.)

D. Decreased water permeability of collecting ducts. (Yes. Water drinking will turn off ADH secretion, less ADH to the collecting ducts and decreased water permeability.)
6. Dehydration: ADH—high, urine volume—low, urine osmolarity—high
   Water drinking: ADH—low, urine volume—high, urine osmolarity—low

7. Countercurrent multiplication and urea recycling

8. Decreased because ADH stimulates both countercurrent multiplication and urea recycling

9. Vasa recta help maintain the corticopapillary gradient; the low blood flow prevents the gradient from being “washed out”

10. Requires corticopapillary gradient and ADH

11. Requires that diluting segments (TALH and early distal) be "diluting" the urine and no or low ADH

12. Inappropriately high H₂O reabsorption in the collecting ducts, too much H₂O is returned to the circulation, dilutes the body fluids. Low serum osmolarity can't turn off ADH secretion, because ADH is secreted "autonomously".

13. Too much H₂O is excreted in urine because no circulating ADH. Loss of "free water" causes concentration of solutes in body fluids.