Glomerular Filtration

Page 1. Introduction

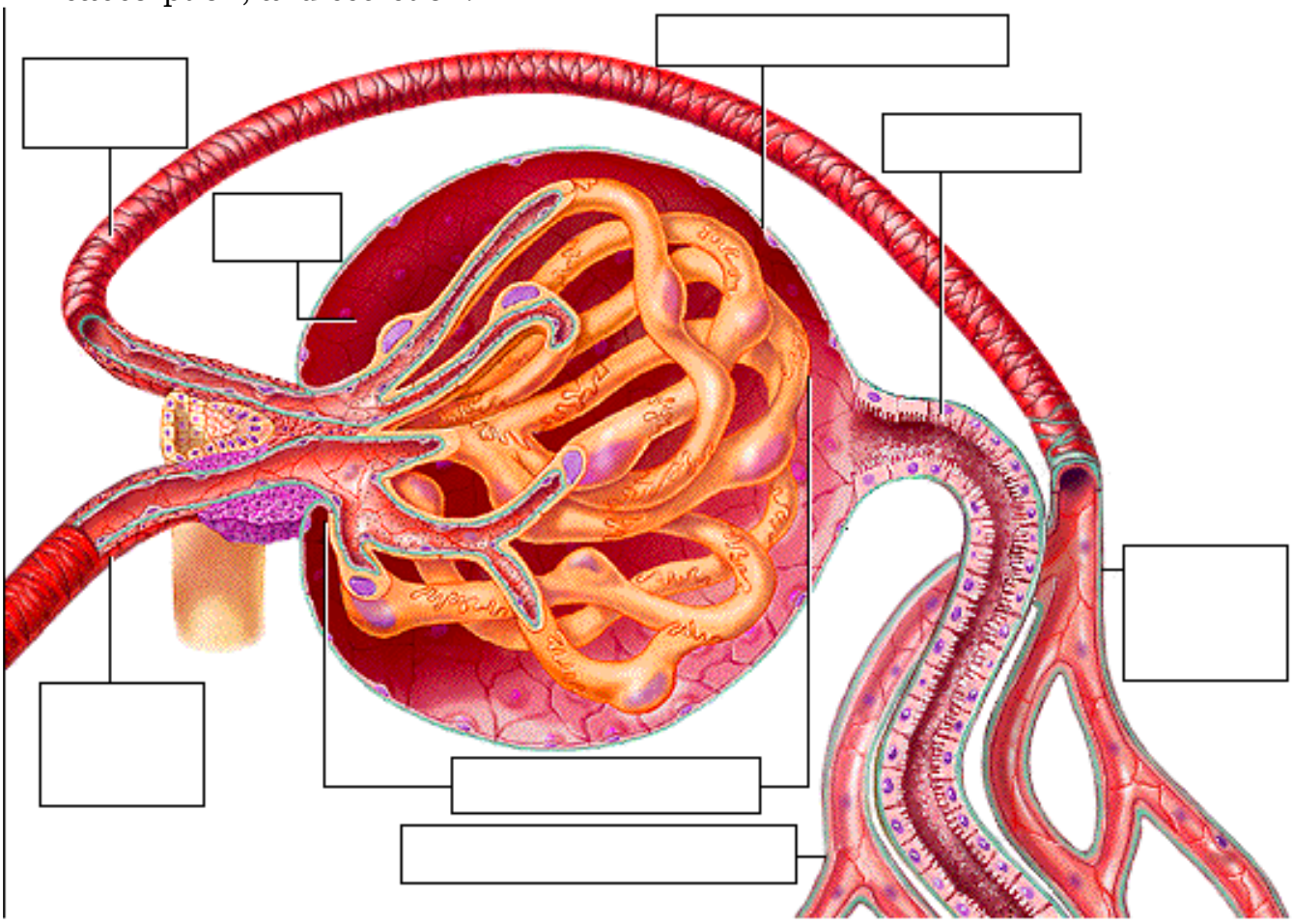
- Formation of urine by the kidney involves three main processes:
  1. filtration
  2. reabsorption
  3. secretion
- During filtration large quantities of water and solutes pass through the filtration membrane from the blood into the glomerular capsule.

Page 2. Goals

- To preview the three major processes of the kidney.
- To understand the function of the filtration membrane.
- To understand the composition of the glomerular filtrate.
- To understand the forces that determine glomerular filtration rate.
- To examine the regulation of glomerular filtration.

Page 3. Renal Processes

- This simplified diagram of a kidney nephron shows the afferent and efferent arterioles, glomerular capsule, capsular space, glomerulus, the beginning of the renal tubule, and peritubular capillaries.
- Label the diagram and draw arrows to indicate the processes of filtration, reabsorption, and secretion:



- **Filtration.** The formation of urine begins with the process of filtration. Fluid and small solutes are forced under pressure to flow from the glomerulus into the capsular space of the glomerular capsule.
- **Reabsorption.** As this filtrate passes through the tubules, specific substances are reabsorbed back into the blood of the peritubular capillaries.
- **Secretion.** In addition, some solutes are removed from the blood of the peritubular capillaries and secreted by the tubular cells into the filtrate to "fine tune" the composition of the blood.
- The rest of this topic covers filtration, while the filtrate processing topics in this module will cover reabsorption and secretion.

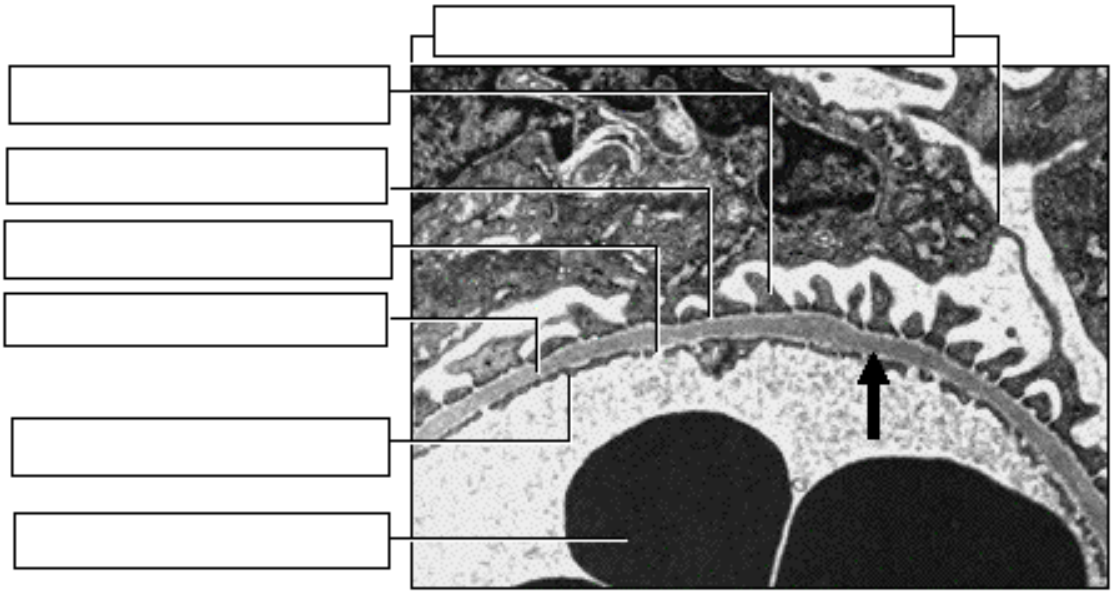
Page 4. The Filtration Process

- A coffee maker provides an everyday example of filtration. The paper filter acts as the filtration membrane. It holds back the large coffee grounds, while letting water and small solutes like caffeine and flavor molecules pass through.
- A force is required to drive this process. In a coffee maker, it's the force of gravity.

- What is the filtration force in the glomerulus? _____

Page 5. The Filtration Membrane and Glomerular Filtration

- Just as a filter keeps grounds out of your coffee, the glomerular filtration membrane keeps blood cells and proteins out of the urine passageways.
- The filtration membrane is composed of three layers:
  1. Fenestrated glomerular endothelium
  2. Basement membrane
  3. Filtration slits formed by pedicels of the podocytes
- Label this diagram:

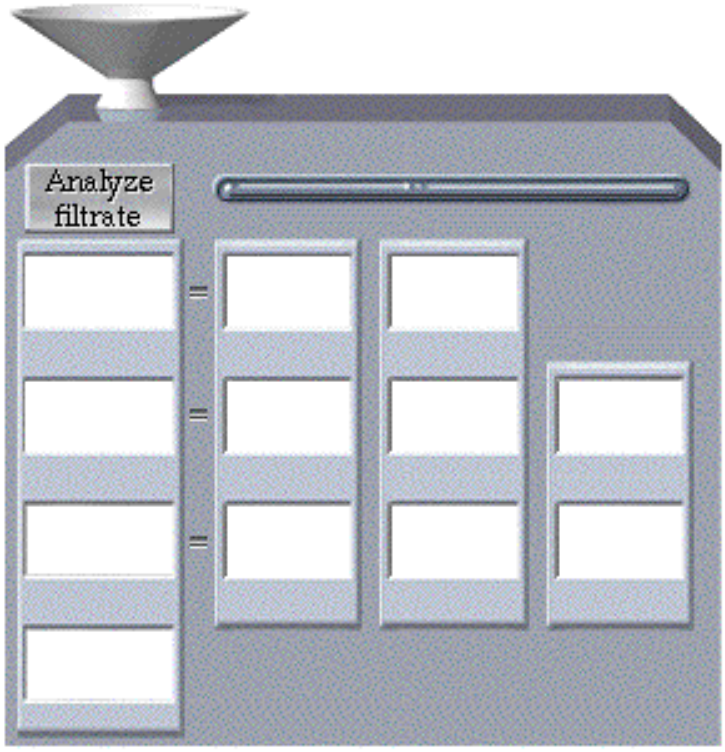


- Passage through the filtration membrane is limited not only on the basis of size but also by charge.
- Glomerular filtration is a process of bulk flow driven by the hydrostatic pressure of the blood.
- Small molecules pass rapidly through the filtration membrane, while large proteins and blood cells are kept out of the capsular space.

- If the filtration membrane is damaged, proteins will leak through and end up in the urine.
- If the filtration membrane is very badly damaged, then blood cells will leak through.
- Consequences of loss of protein in the urine:
  - Loss of albumin causes a decrease in osmotic pressure. Fluid will leak into the interstitial spaces and edema results. Eventually there will be a low circulatory volume and possibly shock.
  - Loss of blood clotting proteins can cause uncontrolled bleeding.
  - Loss of globulins and complement proteins make the individual prone to infection.

Page 6. Glomerular Filtrate

- The fluid and solutes collecting in the capsular space is called glomerular filtrate.
- The concentration of each of these substances in the glomerular filtrate is similar to its concentration in plasma.
- Record the composition of the glomerular filtrate here:



Page 7. Damage to Filtration Membrane

- How might the contents of the filtrate be altered if the filtration membrane is damaged or destroyed? List factors here:

_____

_____

- Presence of protein in the urine is called proteinuria.
- Presence of blood cells in the urine is called hematuria.

** Now is a good time to go to quiz questions 1-2:
- Click the Quiz button on the left side of the screen
- Work through questions 1-2.

- After answering question 2, click the Back to Topic button on the left side of the screen.
- To get back to where you left off, click on the scrolling page list at the top of the screen and choose "8. Forces Affecting Filtration".

Page 8. Forces Affecting Filtration

- There are three forces affecting filtration at the glomerulus:

1. Hydrostatic Pressure within the Glomerular Capillaries

- The blood pressure in the glomerulus averages 60 millimeters of mercury. This unusually high capillary pressure is the result of the short, large diameter afferent arterioles conveying blood at high arterial pressure directly to the glomerular capillaries.
- The smaller diameter of the efferent arterioles leaving the glomerulus also helps maintain the pressure by restricting the outflow of blood.
- However, the glomerular hydrostatic pressure is opposed by two forces that reduce the flow of fluid into the capsular space.

2. Back Pressure from Fluid Within the Capsule

- Fluid already in the capsular space creates a “back pressure” that resists the incoming fluid. This capsular hydrostatic pressure averages 15 millimeters of mercury.

3. Osmotic Pressure within the Glomerular Capillaries

- The second opposing force is the osmotic pressure of the blood in the glomerular capillaries. Remember that the capillaries retain proteins, which become more concentrated in the blood as the filtrate flows out. Because of these proteins, the osmolarity of the blood is higher than the osmolarity of the filtrate. The osmotic pressure of the blood, or its tendency to draw the fluid back in, averages 28 millimeters of mercury.

- The algebraic sum of these three forces produces the net filtration pressure of 17 millimeters of mercury.

  Net Filtration Pressure = 60 mm Hg - (15 mm Hg + 28 mm Hg) = 17 mm Hg

Page 9. Forces Affecting Filtration Analogy

- An analogy for this process would be a football player (#60) trying to run for a touchdown. However, his progress to the goal line is slowed by two opposing players (#15 and #28). The runner eventually reaches the goal, but not as easily as he would without the resistance.
- Now let’s see what happens when a smaller player carries the ball. Click the football to start the process. Here the two opposing forces, players #15 and #28, add together to counteract a smaller, weaker player, #43, stopping his forward progress. This situation is analogous to glomerular hydrostatic pressure too low to overcome the countering forces and carry out filtration. This is referred to as “kidney shut-down” or acute renal failure. Serious consequences will occur unless increased pressure and filtration are resumed.

Page 10. Glomerular Filtration Rate (GFR)

- The total amount of filtrate formed by all the renal corpuscles in both kidneys per minute is called the glomerular filtration rate, or GFR. In normal kidneys, the 17 millimeters of mercury of net filtration pressure produces approximately 125 milliliters of filtrate per minute. This translates to about 180 liters in 24 hours--

nearly enough to fill a 50-gallon barrel! Fortunately, 99% of this volume will be reabsorbed as the filtrate passes through the tubules.

- The glomerular filtration rate is directly proportional to the net filtration pressure, so a fluctuation in any of the three pressures previously discussed will change the GFR. Prolonged changes in normal GFR will cause either too much or too little water and solutes to be removed from the blood.

** Now is a good time to go to quiz question 3:
- Click the Quiz button on the left side of the screen.
- Click on the scrolling page list at the top of the screen and choose "3. Filtration Pressures".
- After answering question 3, click the Back to Topic button on the left side of the screen.
- To get back to where you left off, click on the scrolling page list at the top of the screen and choose "11. Autoregulation of GFR".

Page 11. Autoregulation of GFR

- Fill out this diagram as you work through this page:

	Normal	Mild Exercise	Relaxation
Systemic Pressure			
State of Afferent Arteriole			
Glomerular Hydro-static Pressure			
Net Filtration Rate			

- During **normal conditions**, systemic blood pressure registers approximately 120 millimeters of mercury; the diameter of the afferent arteriole is normal, as is the glomerular hydrostatic pressure. These conditions provide a normal glomerular filtration rate of 125 milliliters per minute.
- When blood pressure fluctuates during normal daily activities, autoregulatory mechanisms of the kidney alter the diameter of the afferent arteriole, in order to maintain a relatively constant glomerular filtration rate.
- During **mild exercise**, the systemic blood pressure increases to 140 millimeters of mercury. If the afferent arteriole remains at the normal diameter, the 17% increase in glomerular hydrostatic pressure will cause a similar increase in GFR [of 21 milliliters per minute, to 146 milliliters per minute]. If allowed to continue, this increase will quickly cause severe dehydration. To avoid extensive fluid loss, the autoregulation mechanism decreases the diameter of the afferent arteriole, decreasing the glomerular blood flow. The glomerular hydrostatic pressure and GFR return to normal, even though the mild exercise continues and the systemic blood pressure remains elevated.
- Reducing the activity level returns the systemic blood pressure to 120 millimeters of mercury; the afferent arteriole dilates to maintain normal glomerular hydrostatic pressure and GFR.
- During periods of **relaxation**, the systemic blood pressure may drop to 100 millimeters of mercury or lower. If the diameter of the afferent arteriole remains normal, blood flow into the glomerulus is reduced. This in turn causes a reduction of glomerular hydrostatic pressure and GFR. To avoid poor filtering of the blood,

the afferent arteriole dilates further to increase blood flow and glomerular hydrostatic pressure. Autoregulation has normalized the GFR.

Page 12. GFR Regulation Mechanisms: Myogenic Mechanism

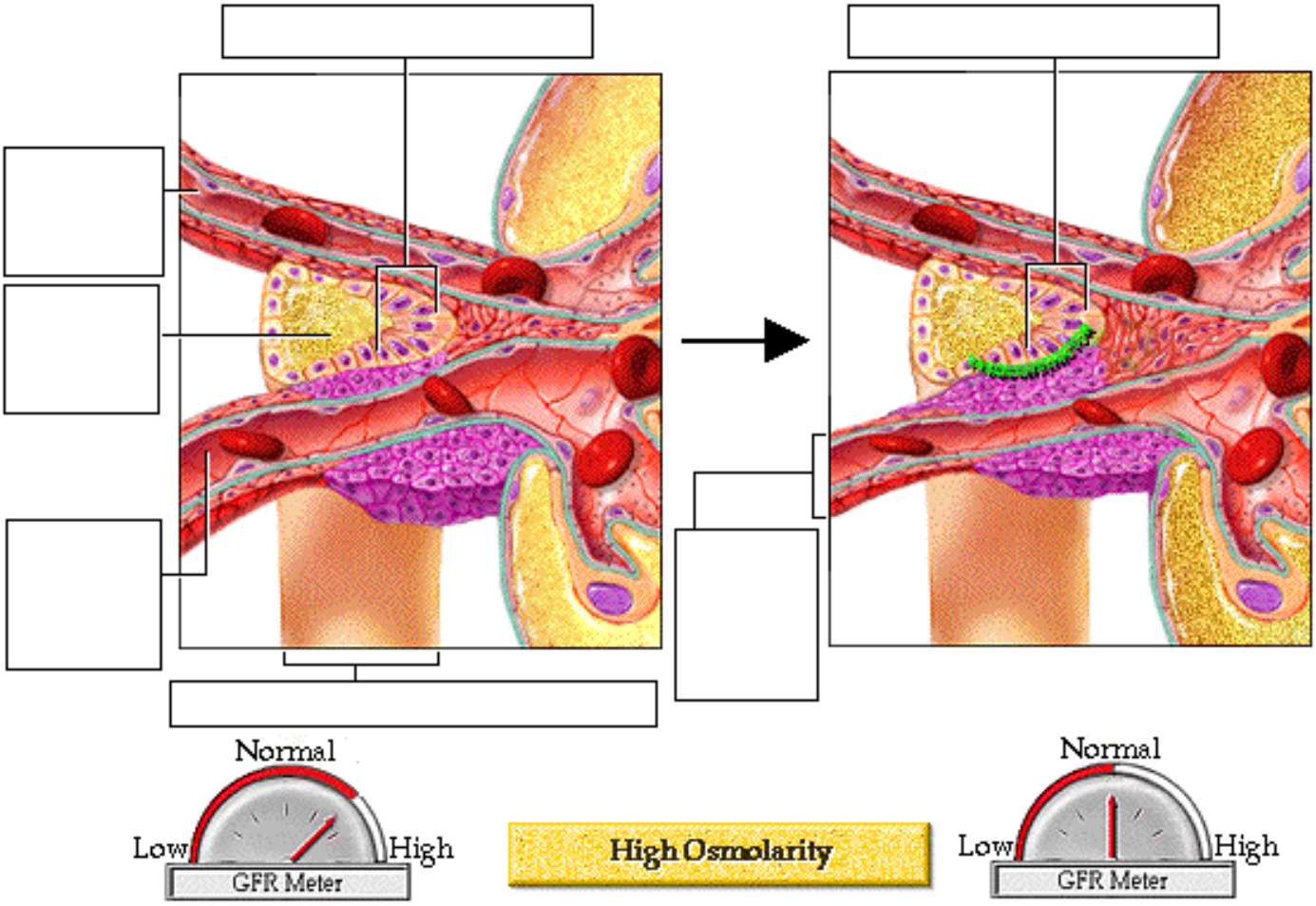
- One of the mechanisms that provides autoregulatory control over renal processes is the result of the inherent tendency of vascular smooth muscle cells to contract when stretched. This allows the diameter of afferent arterioles to respond to changes in blood pressure.
- When blood pressure in an arteriole increases, the walls of the vessel automatically constrict, reducing blood flow through the arteriole.
- Low blood pressure reduces this reflexive constriction, so the arteriole dilates and blood flow is increased.
- In renal autoregulation, this is called the myogenic mechanism.
- Stretching the arteriole wall causes a reflexive vasoconstriction. As long as pressure continues, the vessel will stay constricted.
- When pressure against the vessel wall is reduced, the vessel dilates. Changes in blood pressure therefore directly affect the constriction or dilation of the arteriole, and so glomerular blood flow.
- Fill out this diagram as you work through this page:

	High BP in Afferent Arteriole	**Low BP in Afferent Arteriole**
Effect on Wall of Afferent Arteriole		
Effect on Blood Flow to Glomerulus		

Page 13. GFR Regulation Mechanisms: Tubuloglomerular Mechanism

- A second regulatory mechanism is the sensitivity of the macula densa cells of the juxtaglomerular apparatus to the concentration of sodium chloride in the filtrate, which is proportional to the rate of filtrate flow in the terminal portion of the ascending loop of Henle.

- **High Osmolarity and High Rate of Filtrate Flow in Tubule**.
  - Label the diagram below to indicate what happens when there is a high filtrate osmolarity:



- A higher than normal flow of filtrate, resulting from an increased GFR, causes the concentration of sodium and chloride ions in the filtrate at the end of the ascending limb of the loop of Henle to increase.
  - This high sodium chloride concentration stimulates the macula densa cells to release vasoconstrictor chemicals, which cause the afferent arteriole to constrict.
  - The result is a lower GFR, lower filtrate flow, and increased tubular reabsorption of sodium and chloride ions.
  - Circle the appropriate highlighted word(s) in the chart below:

High GFR

↓

High/Low Filtrate Flow Rate in the Tubules

↓

Increased/Decreased Reabsorption of Ions in the Tubules

↓

High/Low Concentration of Sodium Chloride in the Tubules

↓

Macula Densa Cells **Release/Do Not Release** Vasoconstrictor

↓

Afferent Arteriole **Dilates/Constricts**

↓

GFR **Increases/Decreases**

↓

Filtration Flow Rate **Increases/Decreases**

↓

Increased/Decreased Reabsorption of Ions in the Tubules

↓

Higher/Lower Sodium Chloride Concentration in the Tubules

- **Low Osmolarity and High Rate of Filtrate Flow in Tubule**.
  - A low rate of filtrate flow and, therefore, low sodium chloride in the terminal portion of the ascending loop of Henle is also sensed by the macula densa cells. This condition is usually the result of low GFR caused by low blood pressure.
  - In response, these cells initiate two effects:
    1) They decrease secretion of the vasoconstrictor chemicals. This leads to dilation of the arteriole and so increases blood flow, glomerular hydrostatic pressure, and the GFR
    2) The macula densa cells signal the granular cells of the afferent and efferent arterioles to release renin into the bloodstream.
  - Circle the appropriate highlighted word(s) in the chart below:

Low GFR

↓

High/Low Filtrate Flow Rate in the Tubules

↓

Increased/Decreased Reabsorption of Ions in the Tubules

↓

High/Low Sodium Chloride Concentration in the Tubules

↓

Macula Densa Cells **Release/Do Not Release** Vasoconstrictor

↓

Afferent Arteriole **Dilates/Constricts**

↓

GFR **Increases/Decreases**

↓

Filtration Flow Rate **Increases/Decreases**

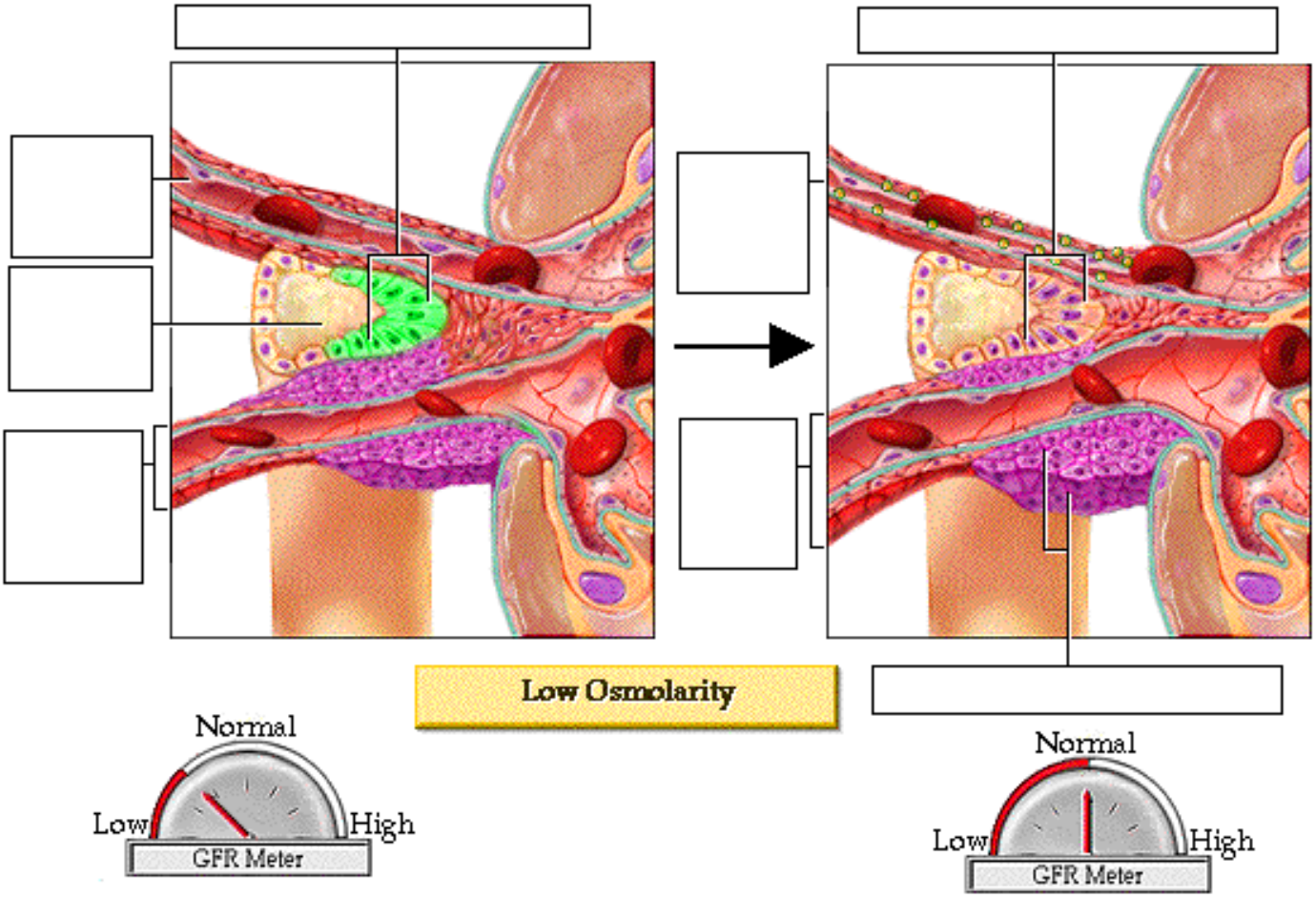
↓

Increased/Decreased Reabsorption of Ions in the Tubules

↓

Higher/Lower Sodium Chloride Concentration in the Tubules

- Label the diagram below to indicate what happens when there is a low concentration of sodium chloride in the filtrate:



- **Effect of Renin on the Regulation of the GFR.** In the bloodstream, renin triggers a series of events that increase the level of the hormone angiotensin II. In the kidney, increased angiotensin II causes constriction of the efferent arteriole. This causes the blood flow out of the glomerulus to slow, thus increasing the glomerular hydrostatic pressure and restoring the glomerular filtration rate to normal. Angiotensin II also stimulates the release of the hormone aldosterone. The effects of aldosterone in the kidney will be discussed in the "Late Filtrate Processing" topic of this module.

Page 14. GFR Regulation Mechanisms: Sympathetic Nervous System Control

- Sympathetic nerve fibers innervate all blood vessels of the kidney as an extrinsic regulation mechanism. During normal daily activity they have minimal influence. However, during periods of extreme stress or blood loss, sympathetic stimulation overrides the autoregulatory mechanisms of the kidney.
- Increased sympathetic discharge causes intense constriction of all renal blood vessels. Two important results occur:
  1) The activity of the kidney is temporarily lessened or suspended in favor of shunting the blood to other vital organs
  2) The lower GFR reduces fluid loss, thus maintaining a higher blood volume and blood pressure for other vital functions. As you can see, renal function has almost stopped.

- Reduction in filtration cannot go on indefinitely, as waste products and metabolic imbalances increase in the blood. Autoregulation mechanisms are now ineffective in preventing acute renal failure.
- When fluid is given intravenously, the blood volume increases. With increasing blood volume, notice the gradual rise in blood pressure, reduction in sympathetic discharge, and restoration of renal functioning.

Page 15. Summary

- Glomerular filtrate is formed by filtration of water and small solutes through the filtration membrane.
- Net filtration pressure is the glomerular hydrostatic pressure minus the opposing forces of capsular hydrostatic pressure and glomerular osmotic pressure.
- Blood pressure and flow in the nephron is monitored and controlled by renal autoregulation mechanisms in order to maintain a relatively steady glomerular filtration rate.
- During periods of severe blood loss, the sympathetic nervous system overrides the renal autoregulatory mechanisms to shunt the blood to other critical areas.

** Now is a good time to go to quiz question 4:
- Click the Quiz button on the left side of the screen.
- Click on the scrolling page list at the top of the screen and choose "4. Autoregulation".

Notes on Quiz Questions:

Quiz Question #1: Filtration Membrane

- This question asks you to identify the layers of the filtration membrane.

Quiz Question #2: Filtrate Contents

- This question asks you to identify the components of filtrate

Quiz Question #3: Filtration Pressures

- This question asks you to identify the types of pressures affecting GFR and predict some of the factors influencing these pressures.

Quiz Question #4: Autoregulation

- This question asks you to predict if the efferent and afferent arteriole will vasoconstrict or vasodilate based on blood pressure. You may want to fill out this chart as you work through this question:

	Condition A	**Condition B**	**Condition C**	**Condition D**
Blood Pressure				
Efferent Arteriole				
Afferent Arteriole				

Study Questions on Glomerular Filtration:

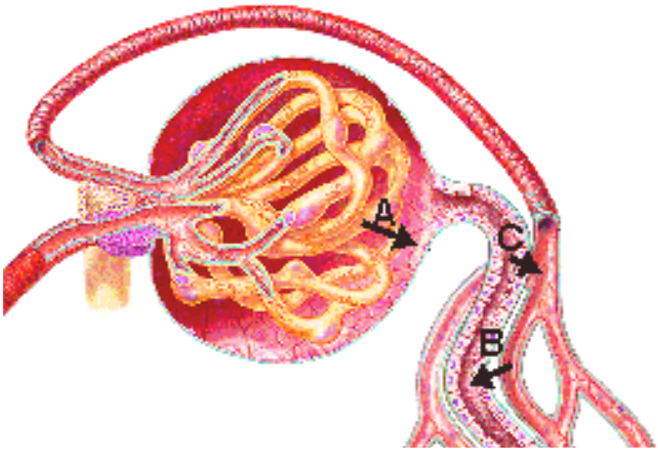
1. (Page 1,3.) What are the three processes in the formation of urine?

2. (Page 3.) Briefly describe the movement of fluid during filtration. What part of the nephron and what capillaries are involved?

3. (Page 3.) Briefly describe the movement that occurs during reabsorption. What part of the nephron and what capillaries are involved?

4. (Page 3.) Briefly describe the movement that occurs during secretion. What part of the nephron and what capillaries are involved?

5. (Page 3.) In this diagram, identify which arrows correspond to the process of filtration, reabsorption, and secretion.



6. (Page 4.) What is the filtration force in the glomerulus?

7. (Page 5.) List the three layers of the filtration membrane.

8. (Page 5.) What is the main factor that determines what passes through the filtration membrane?

9. (Page 5.) Blood can be divided into particles, based on size: blood cells, protein, and small molecules and ions. Which of these can freely pass through the filtration membrane?

10. (Page 5.) What process drives filtration?

11. (Page 5.) If the filtration membrane is damaged and protein is lost in the urine, what effect would the loss of the following plasma proteins have on the body?
    a. albumin b. blood clotting proteins c. globulins and complement

12. (Page 6.) What is the fluid called that collects in the capsular space?

13. (Page 6.) What are the four main categories of components of the glomerular filtrate?

14. (Page 6.) Give two examples of organic molecules that are filtered at the glomerulus.

15. (Page 6.) Give three examples of nitrogenous wastes that are filtered at the glomerulus.

16. (Page 6.) Give three examples of ions that are filtered at the glomerulus.

17. (Page 6.) The concentration of substances within the glomerular filtrate are similar to the concentration of substances in the ____.

18. (Page 8.) What are three forces affecting filtration at the glomerulus. In which direction (towards the blood or towards the filtrate) does each of the forces push fluid?

19. (Page 8.) Why is the blood pressure in the glomerulus so high?

20. (Page 8.) Why is there more osmotic pressure in the glomerular capillaries than in the filtrate?

21. (Page 8.) Calculate the net filtration pressure at the glomerulus when the hydrostatic pressure is 60 mm Hg, the back pressure is 15 mm Hg, and the osmotic pressure is 28 mm Hg.

22. (Page 10.) What is the term used for the total amount of filtrate formed by all the renal corpuscles in both kidneys per minute?

23. (Page 10.) What happens to most of the approximately 180 liters of fluid filtered at the glomerulus each day?

24. (Page 10.) What increases or decreases the GFR?

25. (Page 11.) When blood pressure fluctuates during normal daily activities, how does the kidney maintain a relatively constant glomerular filtration rate?

26. (Page 11.) What happens to the diameter of the afferent arteriole during mild exercise? What happens to the GFR?

27. (Page 11.) What happens to the diameter of the afferent arteriole during relaxation? What happens to the GFR?

28. (Page 12, 13, 14) What are the two autoregulatory mechanisms that influence the glomerular filtration rate?

29. (Page 12.) According to the myogenic mechanism for regulation of the glomerular filtration rate, what happens to the afferent arteriole and blood flow to the glomerulus when the wall of afferent arteriole is stretched due to a high blood pressure?

30. (Page 12.) According to the myogenic mechanism for regulation of the glomerular filtration rate, what happens to the afferent arteriole and blood flow to the glomerulus when the wall of afferent arteriole experiences a low blood pressure?

31. (Page 13.) What three factors trigger the tubuloglomerular mechanism for regulation of the glomerular filtration rate?

32. (Page 13.) What does a high concentration of sodium chloride in the terminal portion of the ascending loop of Henle indicate?

33. (Page 13.) What does a low concentration of sodium chloride in the terminal portion of the ascending loop of Henle indicate?

34. (Page 13.) When there is a high glomerular filtration rate, the tubuloglomerular mechanism acts to decrease the GFR. Circle the appropriate highlighted words in the first flowchart on page 13 to explain how this works.

35. (Page 13.) When there is a low glomerular filtration rate, the tubuloglomerular mechanism acts to increase the GFR. Circle the appropriate highlighted words in the second flowchart on page 13 to explain how this works.

36. (Page 13.) What cells produce and secrete renin?

37. (Page 13.) When is renin released?

38. (Page 13.) What is the effect of renin?

39. (Page 13.) What is the effect of constriction of the efferent arteriole?

40. (Page 14.) When does the sympathetic nervous system override the autoregulatory mechanisms of the kidney?

41. (Page 14.) What is the effect of the sympathetic nervous system on the kidney?

Early Filtrate Processing

Page 1. Introduction

- Once the filtrate is formed, the early tubular segments of the nephron reabsorb solutes and water back into the blood to restore its volume and composition.
- They also remove some solutes from the blood and secrete them into the filtrate to fine tune the blood's composition.

Page 2. Goals

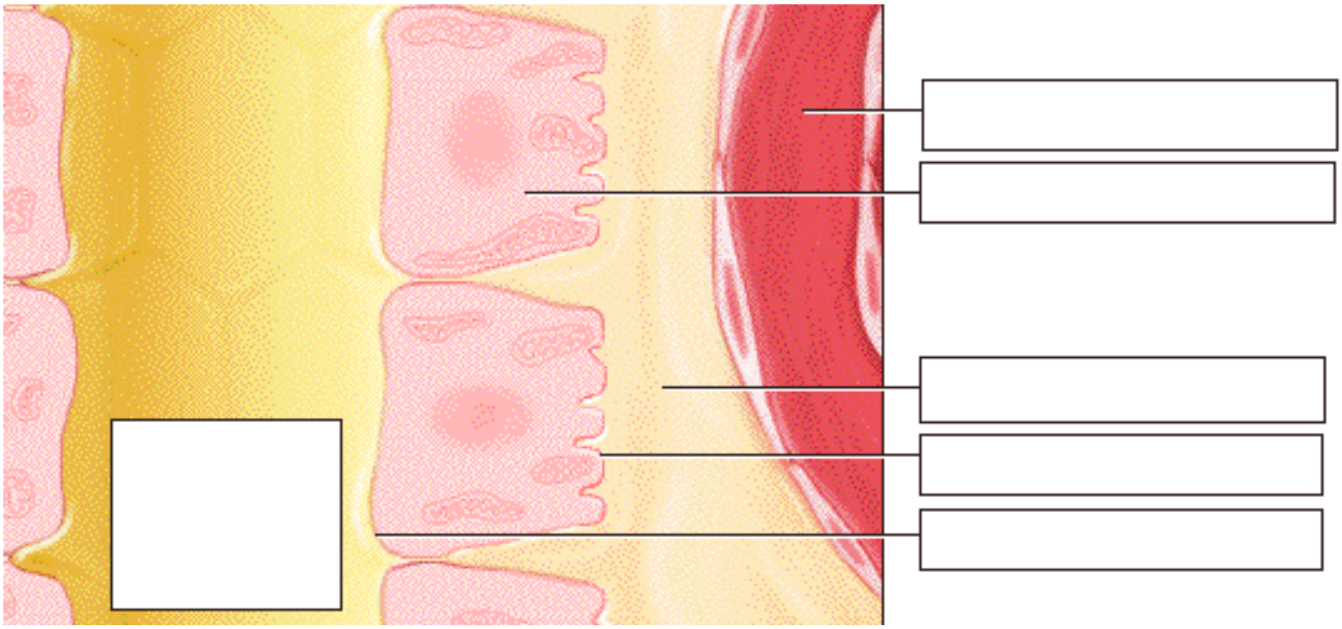
- To examine the passive and active processes of reabsorption and secretion
- To understand how filtrate processing differs in early sections of the tubule.
- To understand the role of the countercurrent multiplier in forming the medullary osmotic gradient

Page 3. Reabsorption: Reclaiming Valued Substances

- The relationship of glomerular filtration and tubular reabsorption is something like a parent who cleans a child's room by arbitrarily throwing much of the room's contents into the trash box. That's analogous to glomerular filtration. But as soon as the parent is gone, the child quickly reclaims his favorite things from the box. This rescue of 'valued substances' is like the process of tubular reabsorption of solutes back into the blood. All objects remaining in the trash box will be discarded as waste.

Page 4. Reabsorption Pathways

- To be reabsorbed into the blood, substances in the filtrate must cross the barrier formed by the tubular cells.
- There are two reabsorption pathways:
  1. the transcellular pathway
  2. the paracellular pathway
- Most solutes that are reabsorbed use the transcellular pathway. They diffuse or are actively transported through the luminal and basolateral membranes of the tubular cells into the interstitial space and then into the peritubular capillaries.
- The second pathway is the paracellular one through the tight junctions into the lateral intercellular space. Certain tight junctions are not as tight as the name implies and will allow this pathway, while others will not.
- Although most substances use the transcellular pathway, water and certain ions use both paths, especially in the proximal convoluted tubule. Both pathways lead into the interstitial space, then through the endothelium of the peritubular capillaries into the blood.
- Label this diagram and using arrows indicate both the transcellular and paracellular pathways:

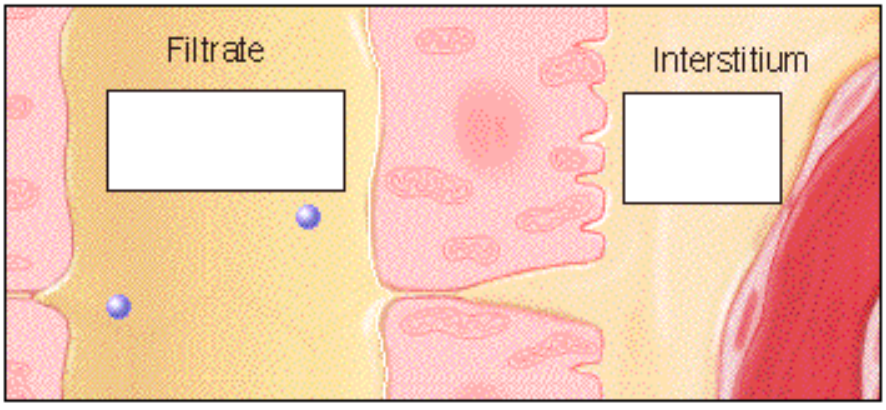


Page 5. Reabsorption Overview: Diffusion of Water

- The force driving the formation of the filtrate is blood pressure within the glomerulus.
- What drives reabsorption, which reclaims the valued substances?
- How water to diffuses from the lumen through the tight junctions of these generic tubular cells into the interstitial space:
  1. Water will move from its higher concentration in the tubule through the tight junctions to its lower concentration in the interstitium.
  2. Water will also move through the plasma membranes of the cells that are permeable to water.

** Notice that they use a darker color to indicate a higher osmolarity.

- On this diagram, indicate:
  1. Where the water concentration is highest and lowest.
  2. Where the osmolarity is higher and lower.



Page 6. Reabsorption Overview: Interstitial Osmolarity

- How can we increase the osmolarity of the interstitium?
- Transporting sodium into the interstitium will raise its osmolarity. Water will then diffuse from the tubule through the tight junctions and permeable plasma membranes to the interstitium, equilibrating the two osmolarities.

Page 7. Reabsorption Overview: Membrane Activity

- How will the reduction in the intracellular sodium ion concentration resulting from the basolateral transport affect the activity at the luminal membrane?
- The transport of sodium ions through the basolateral membrane will cause more ions to be reabsorbed through the luminal membrane.

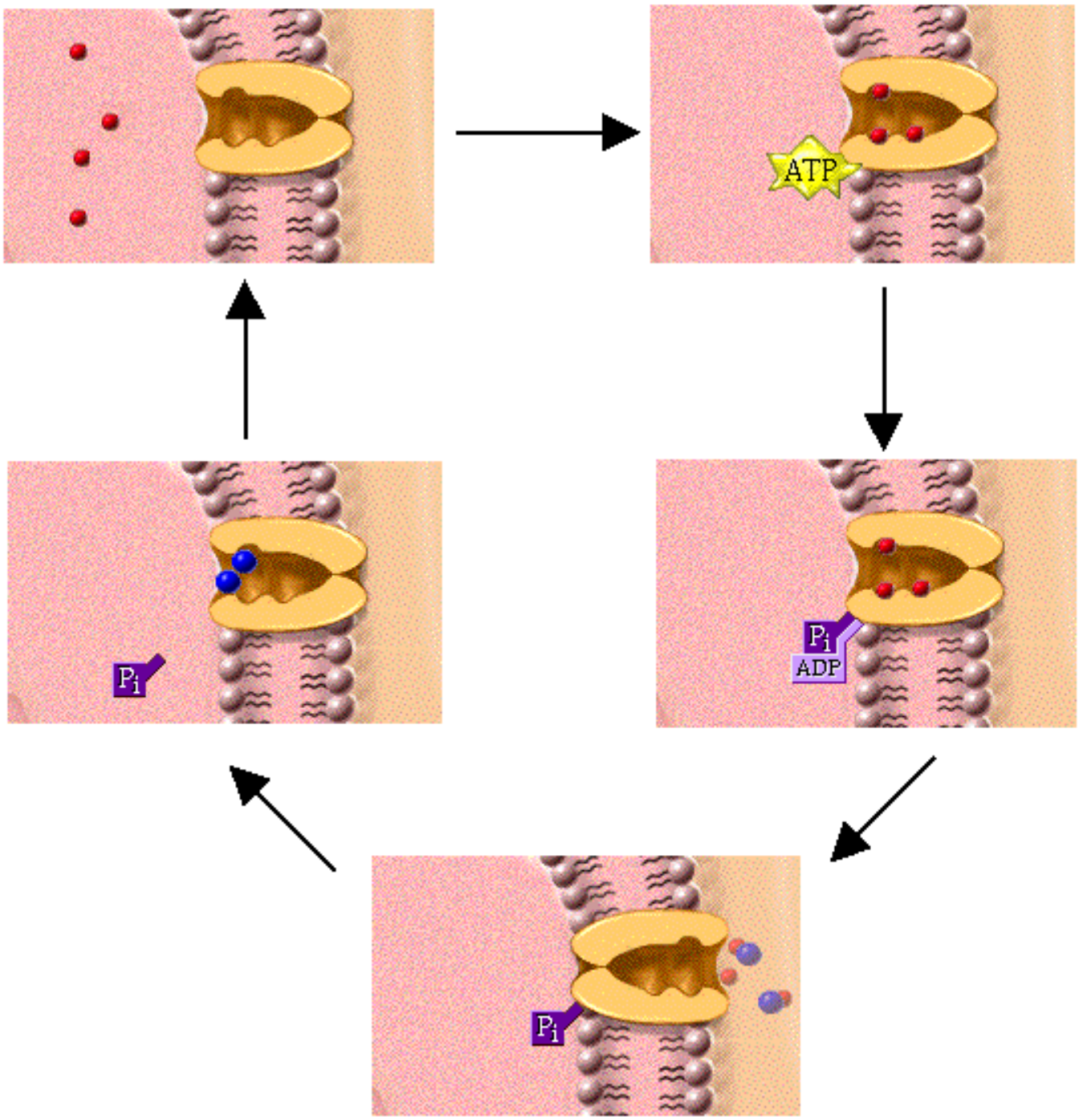
Page 8. Reabsorption Overview: Summary

- The transport of sodium ions has two important direct results:
  1) The interstitial osmolarity increases, causing water to diffuse out of the tubular lumen
  2) the lowered intracellular concentration causes additional sodium ions to be reabsorbed through the luminal membrane.
- This provides more sodium ions to be actively transported and enables the cycle to repeat.
- In addition sodium ion transport enables the reabsorption of most substances in the nephron.

Page 9. PCT Basolateral Membrane: Active Transport

- The renal tubules are composed of specialized cells in each region that accomplish a different stage of filtrate processing.
- The proximal convoluted tubule is where major reabsorption of valued substances occurs. We'll look first at the activities occurring at the basolateral membrane of the tubular cells.
- The reabsorption of many substances from the glomerular filtrate in the PCT depends directly or indirectly on the active reabsorption of the sodium ion.
  - The cellular structure responsible for this process is the sodium/potassium ATPase ion pump located in the basolateral membrane.
  - Using energy from ATP, the ion pump carries out primary active transport of sodium ions out of the cell and potassium ions into the cell.
  - As it yields its energy, ATP is converted to ADP and an inorganic phosphate ion, or P_i.
- The sodium-potassium pump is found in the basolateral membrane of many regions of the nephron.

- As you watch the animation of the sodium potassium pump, describe what is happening between each picture in the diagram below:



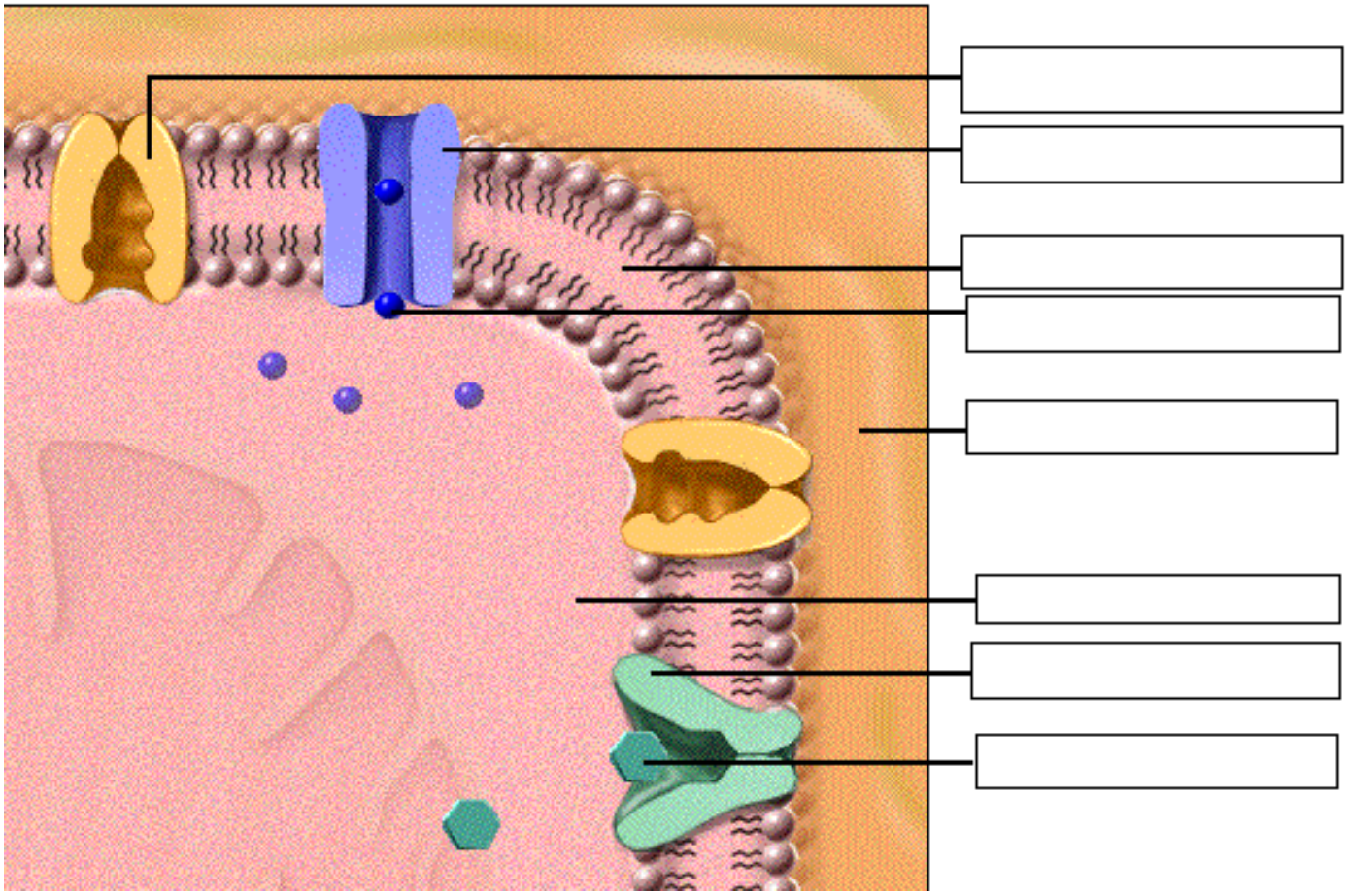
- Watch what happens to the fluid in the interstitial space as a result of the ion pump's activity. Notice that the interstitial fluid is becoming more concentrated, as indicated by the darker color. The net effect of the ion pump's activity is to decrease the sodium ion concentration inside the cell and increase its concentration outside the cell, thereby increasing the interstitial osmolarity.
- This increased osmolarity around the PCT soon draws water from the tubule, decreasing the interstitial osmolarity again, and together the water and solutes diffuse passively into the peritubular capillaries and are carried away.

Page 10. PCT Basolateral Membrane: Diffusion

- There are two additional transmembrane proteins in the basolateral membrane:

1. a potassium ion channel
2. a glucose carrier molecule

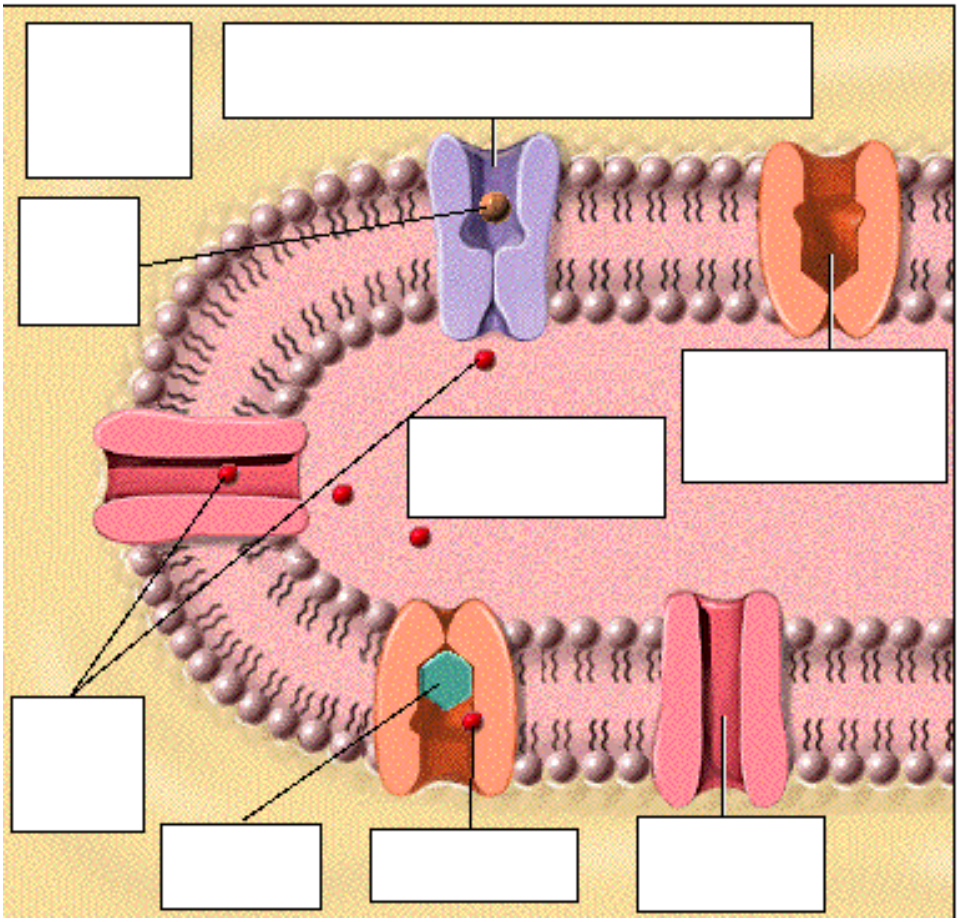
- The glucose carrier molecule binds only to glucose, and transports it across the basolateral membrane by a passive mechanism called facilitated diffusion. Glucose can move either into or out of the cell, depending on its concentration. Since in the situation shown here, its concentration is highest in the cell, glucose moves out of the cell into the interstitium.
- The potassium ion channel lets most of the potassium ions diffuse from the tubular cells back into the interstitium. It prevents the sodium-potassium ATPase ion pump from causing potassium ion depletion in the blood or excess accumulation in the cells.
- In addition to the molecules you see here, many other substances also cross the basolateral membrane by similar mechanisms.
- Label the parts of this diagram:



Page 11. PCT Luminal Membrane Activity

- The luminal membrane of the proximal convoluted tubule contains many transport proteins.
  - Here you see three sodium-hydrogen countertransport carrier molecule, and two sodium/glucose cotransport carrier molecules.
  - The activity of all these carrier molecules depends on sodium-potassium ATPase ion pump activity in the basolateral membrane.

- **Sodium Channels.** The sodium ion concentration of the cytosol has been lowered by the activity of the sodium/potassium pumps in the basolateral membrane. As a result, additional sodium ions move from the high extracellular concentration in the filtrate through the luminal membrane to the low intracellular concentration in the cytosol. They are transported by simple diffusion through sodium channels, and they then move to the basolateral membrane and are pumped into the interstitium as you have seen.
- **Sodium-Hydrogen Countertransport Molecule.** The countertransport (or antiport) carrier molecule carries a sodium ion into the cell, and in exchange secretes a hydrogen ion into the filtrate. Here in the PCT, this activity is dependent on the movement of a sodium ion down its concentration gradient from high extracellular to low intracellular concentrations. This is an example of secondary active transport driven by the primary active transport of the basolateral membrane. The hydrogen ion being secreted here is generated in the cell for acid/base balancing purposes.
- **Sodium-Glucose Cotransport Carrier Molecule.** The cotransport (or symport) carrier molecules carry both sodium and glucose into the cell. The reabsorption of glucose depends on the movement of a sodium ion down its concentration gradient from high extracellular to low intracellular concentrations. This is an example of secondary active transport. Glucose now moves down its concentration gradient to the basolateral membrane, where it is transported into the interstitium by facilitated diffusion as seen previously.
- Label this diagram and indicate the direction of movement of glucose, sodium, and hydrogen ion:



- This animation shows only a few of the molecules that cross the luminal membrane of the PCT. Although not shown here, water and many other solutes diffuse or are actively transported through the luminal membrane for reabsorption back into the blood.
- **Transport Maximum, or T_m.** For most actively reabsorbed solutes, the amount reabsorbed in the PCT is limited only by the number of available transport carriers for that specific substance. This limit is called the transport maximum, or T_m. If the amount of a specific solute in the filtrate exceeds the transport maximum, the excess solute continues to pass unreabsorbed through the tubules and is excreted in the urine.

Page 12. The Effect of Hyperglycemia

- Glucose is vital to the body's normal functioning. However, in hyperglycemia, a condition that accompanies the disease diabetes mellitus, excess glucose accumulates in the blood.
- If the number of cotransport molecules is not sufficient to handle an abnormally high concentration of glucose in the filtrate, the transport maximum is exceeded and the 'extra' glucose will be excreted in the urine.

Page 13. Glucose Reabsorption Analogy

- The concept of transport maximum is much like this factory analogy. A fixed number of workers is matched to the maximum number of sacks of sugar they can remove from a moving conveyor belt. Under normal conditions all sugar is removed, because the number of workers and their rate of work is adequate to remove all of the sacks from the belt.
- If the number of sacks moving down the belt is increased, the workers cannot handle the extra load while working at their normal rate. They will remove only their "normal" amount, and the excess sugar will end up as waste.
- In the condition of hyperglycemia resulting from diabetes mellitus, excess sugar in the filtrate exceeds the transporting capacity of the available carriers in the cells of the proximal convoluted tubule. Therefore, some of the sugar is not reabsorbed and so is excreted in the urine.

Page 14. PCT Paracellular Pathway

- The second reabsorption route, the paracellular pathway, uses the small space between cells as a passageway.
- The tight junctions of the proximal convoluted tubule are not as tight as their name implies. The increased osmolarity of the fluid in the lateral intercellular spaces, resulting from sodium-potassium ATPase ion pump activity, causes water to diffuse from the tubular lumen through the paracellular pathway.
- As this water moves, sodium, chloride, and potassium ions may also follow passively in a process called solvent drag. A large percentage of potassium and chloride ions are reabsorbed in this manner.
- Notice that the flow of water into the lateral intercellular space reduces the osmolarity of the interstitial fluid, so that it equilibrates with the osmolarity of the filtrate.

Page 15. Summary of Reabsorption in the PCT

- To summarize the activities of the proximal convoluted tubule:

- Sodium/potassium ATPase ion pumps in the basolateral membrane drive the reabsorption of water and solutes by increasing the sodium ion concentration of the interstitium.
- Hydrogen ions are secreted into the filtrate to provide an acid/base balance.
- Abundant channels and transport molecules in the luminal membrane provide passage for solutes to move down their concentration gradients between the filtrate and the cytosol of the cell.
- Water and solutes move by bulk flow from the interstitium into peritubular capillaries to complete their reabsorption process.

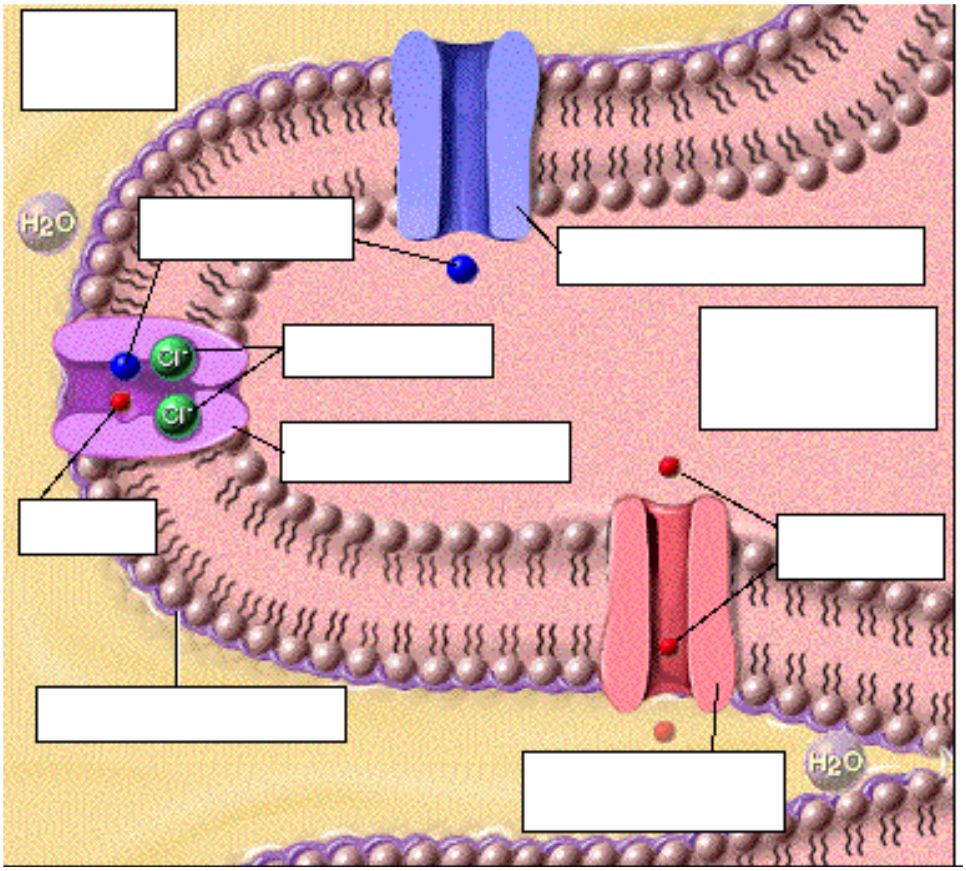
- As a result, valued substances have been reclaimed. Approximately 65% of the filtrate is reabsorbed into the peritubular capillaries from the PCT. Included in this reabsorbed volume is virtually 100% of the filtered glucose, amino acids, and any proteins that may have escaped from the glomerulus.

Page 16. Reabsorption in Thin Descending Loop of Henle

- As the tubule transitions from the proximal convoluted tubule to the thin, descending loop of Henle, it straightens and dips into the medulla, and its epithelium changes from cuboidal to flattened squamous cells.
- As in the PCT, the cells here are permeable to water, allowing diffusion in response to osmotic gradients. The increasingly high osmolarity of the medullary interstitium provides a strong osmotic gradient that pulls water out of the filtrate.
- Sodium ions, chloride ions, and most solutes cease to be reabsorbed in this region, because the flattened cells lack transport proteins. As a result of these conditions, a great deal of water leaves the filtrate, while solutes are retained. This causes the filtrate to become increasingly more concentrated as it passes down the tube.

Page 17. Luminal Membrane Reabsorption in Ascending Loop of Henle

- Label this diagram. Draw arrows to show direction of ion movement:



- As the loop of Henle ascends toward the cortex, the thin squamous cells transition to simple cuboidal cells of the thick ascending limb.
- Water permeability of these cells is greatly restricted by tight junctions and by a glycoprotein layer that covers the luminal membrane.
- Looking at the luminal membrane of these cells, we see that they lack a brush border, in contrast to the cells of the proximal convoluted tubule. However, they do have a limited number of short microvilli containing many ion channels and secondary active transport molecules.
- Notice that this secondary active transport molecule is not the same carrier as the sodium/glucose cotransporter in the PCT. Instead, this carrier molecule cotransports a potassium ion and two chloride ions. However, just as with the sodium/glucose cotransporter, it is the sodium ion moving down its concentration gradient that drives this activity. The import of potassium does not increase the cell's potassium concentration, because these ions diffuse back into the filtrate through the potassium ion channels in the luminal and basolateral membranes. As we shall see on the next page, the imported chloride ions follow the sodium ions through the cytosol to the basolateral membrane.

Page 18. Basolateral Membrane Reabsorption in the Ascending Loop of Henle

- The cells in the basolateral membrane possess the same sodium-potassium ATPase ion pumps and potassium channels as do the cells of the proximal convoluted tubule. These pumps generate a sodium ion concentration gradient that drives the reabsorption of other substances through the luminal membrane.
- Notice also the chloride channel, which allows chloride ions entering from the luminal membrane to follow sodium ions out of the cell.
- The increasing osmolarity of the interstitial fluid is the result of sodium, chloride, and potassium ions being reabsorbed from the filtrate and transported into the

interstitial space. The restricted diffusion of water out of the filtrate, prevents equilibration of the filtrate and interstitial fluid.

- The cells of the ascending limb of the loop of Henle are able to maintain an osmotic difference between these two fluids of approximately 200 milliosmoles.

Page 19. Summary of Ascending Limb of the Loop of Henle Activity

- Label the processes (A-C) in this diagram. Also show the milliosmoles at each place in the ascending loop of Henle:

A. _____

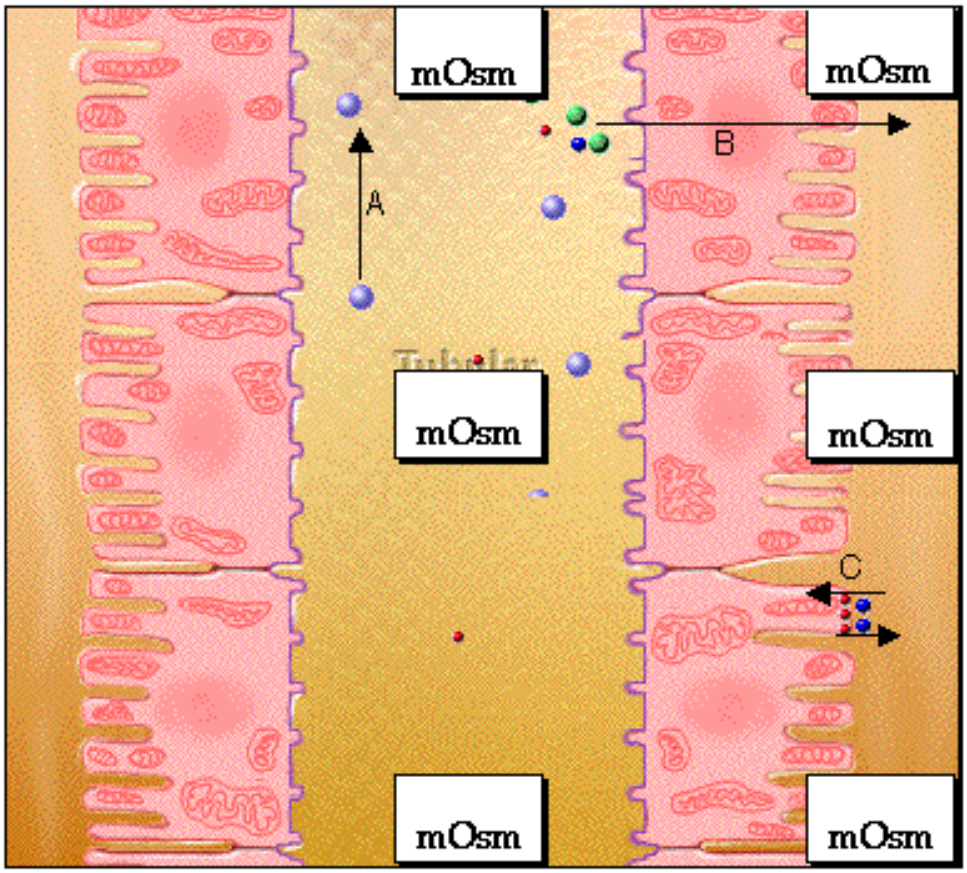
_____

B. _____

_____

C. _____

_____



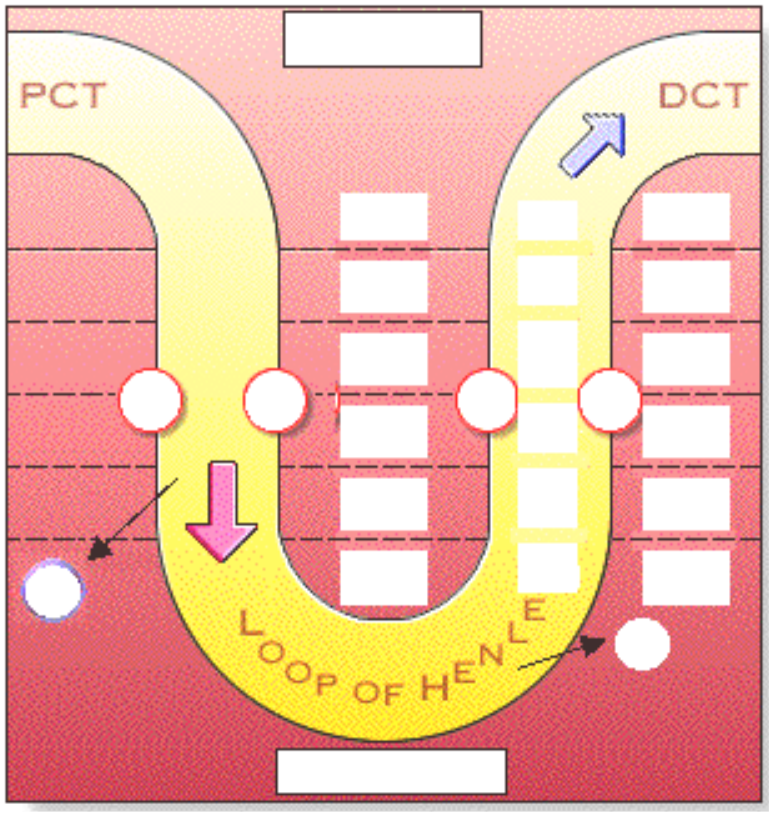
- In summary, as a result of solutes being removed from the filtrate and water being retained, there are two very important effects:
  1) The filtrate becomes increasingly dilute as it moves up the tubule.
  2) The osmolarity of the interstitium is 200 milliosmoles greater than the osmolarity of the filtrate at any given level of the tubule.
- Notice particularly that this has also formed an osmolarity gradient from the bottom of the interstitium to the top. In this medullary osmotic gradient, the osmolarity of the deeper region is greater than that of the region close to the cortex.

Page 20. The Loop of Henle: A Countercurrent Multiplier

** There are many pauses on this page. Make sure you don't click the Next button until all the animations are finished.

- To demonstrate the current theory of how the loop of Henle forms the medullary osmotic gradient, here's a simplified view of the cortex and medulla.
- This theory is called the countercurrent theory because of the opposing flow of filtrate within the two limbs of the loop.

- The complex interplay of the ascending and descending limbs forms and maintains an interstitial osmolarity with a gradient from approximately 1200 milliosmoles near the bottom of the loop to the normal 300 milliosmoles near the cortex. The gradient formed by this activity is essential for the concentration of urine.
- Label this diagram:

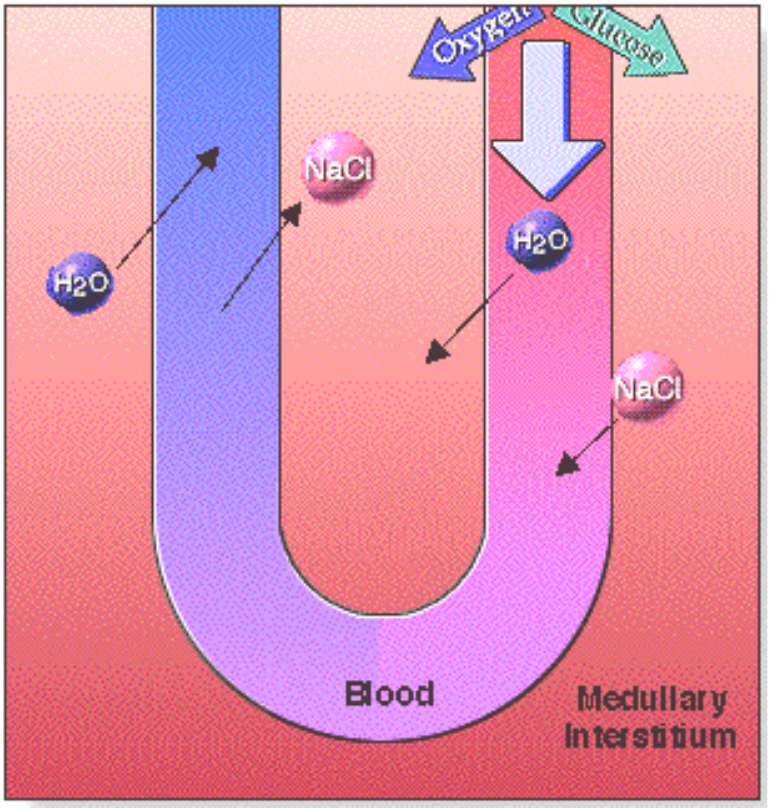


- **Ascending Limb.**
  - To demonstrate how the gradient is formed, we will look first at the role of the ascending limb of the loop and then at that of the descending limb, because the ascending limb creates the conditions necessary for the descending limb to function.
  - The ascending limb of the loop actively transports sodium chloride into the interstitium, increasing its concentration, while restricting the diffusion of water.
  - The interstitium surrounding the tubule becomes more concentrated, while the fluid inside becomes more dilute.
  - As the fluid moves up the loop there is progressively less solute to pump out, so the highest concentrations of solutes are near the bottom of the loop.
- **Descending Limb.**
  - The role of the descending limb in this process is to provide a continuous, concentrated supply of sodium chloride to the ascending limb.
  - The filtrate concentrates as it moves down the descending limb, because water diffuses into the higher osmolarity interstitium created by the ascending limb.
  - The solutes remaining in the tube reach a concentration approximately four times greater than normal body fluid. The effect is much like what happens in the Great Salt Lake when water evaporates and salt is left behind; the fluid that is left is very salty.
  - This salty filtrate provides a ready supply of sodium chloride for the ascending limb to maintain the osmotic gradient.

- **Combined Activities.**
  - The way the two limbs cooperate to multiply the solute concentration from the normal 300 milliosmoles of the cortex to a level four times higher in the medulla is called the countercurrent multiplier mechanism.
  - This mechanism has also diluted the luminal fluid in the ascending limb to an osmolarity of approximately 100 milliosmoles; as a result, water is retained, while solutes are removed. This graphic now shows the 200 milliosmole difference between filtrate and interstitium developed by the cells of the thick ascending limb.

Page 21. The Vasa Recta: A Countercurrent Exchanger

- How are the solutes in the medullary interstitium kept from being carried away by the blood? The cells of the medulla require nutrients to function properly; however, blood in a normal capillary flowing through the medulla would also reabsorb and remove massive amounts of solutes from the medullary interstitium. This would quickly weaken the osmotic gradient. To avoid this problem, the capillaries of the vasa recta form 'hair pin' loops enabling them to function as countercurrent exchangers.
- Blood in the vasa recta loops delivers nutrients such as glucose and oxygen to the cells of the region.
- At the same time, the loops function as countercurrent exchangers of sodium chloride and water.



- The exchange mechanism works as follows:
  1. Blood moving down the descending portion of the vasa recta loop passes through areas of increasing osmolarity.
  2. Responding to osmotic pressure, water diffuses out of the blood into the interstitium.

3. At the same time, sodium and chloride ions diffuses into the blood as a result of its higher concentration in the interstitium.
4. If this blood now left the medulla, the sodium and chloride ions would be removed and lost to the osmotic gradient. However, the capillary actually reverses direction, so the conditions also reverse.
5. The viscous blood moves up the ascending portion of the vasa recta through areas of decreasing osmolarity. The blood regains the water by osmosis and loses most of the solutes back into the interstitium.

- The net result is that the blood has brought nutrients to the cells of the medulla without carrying away extensive amounts of solute, which would weaken the osmotic gradient.

Page 22. Summary

- 65% of the filtrate is reabsorbed in the proximal convoluted tubule through active and passive transport processes**.**
- The filtrate is concentrated in the descending loop of Henle; water is lost while solutes are retained.
- The filtrate is diluted in the ascending loop of Henle; solutes are lost while water is retained.
- The asymmetrical pattern of water and sodium chloride reabsorption in the ascending and descending loop of Henle creates an osmotic gradient within the medullary region.
- The vasa recta circulate blood through the medulla to provide nutrients without removing solutes and weakening the osmotic gradient.

** Now is a good time to go to quiz questions 1-11:
- Click the Quiz button on the left side of the screen.
- Work through quiz questions 1-11. Fill in the charts below as you answer the questions.

Notes on Quiz Questions:

Quiz Question #1: Tubular Permeability Characteristics

- This question asks you to rate the permeability of the PCT, descending loop of Henle, and ascending loop of Henle to water, ions, and glucose. Fill out this chart as you do this question:

	Permeability to Water	**Permeability to Na^+ and Cl^- Ions**	**Permeability to Glucose**
Proximal Convoluted Tubule			
Descending Loop of Henle			_____
Ascending Loop of Henle			_____

Quiz Question #2: Descending and Ascending Loop of Henle

- This question asks you to choose what will happen to water , ions, and filtrate in the ascending and descending limb of the loop of Henle. Fill out this chart as you do this question:

	Descending Loop of Henle	**Ascending Loop of Henle**
Sodium & Chloride Ions		
Water		

Filtrate		

Quiz Question #3: Membrane Transport Trivia

- This question asks you to classify various membrane transporters. Fill in this diagram as you do the question:

Transport Model							
Substance Transported							
Membrane Location							
Transport Mechanism							
Transport Method							

Quiz Question #4: Effects of Furosemide

- This question asks you to predict what will happen if a drug is given that will block ion reabsorption in the ascending limb of the loop of Henle.

Quiz Question #5: Increase/Decrease Furosemide

- This question asks you to predict the effect of the drug on the body.

Quiz Question #6: Glucose and Sodium Reabsorption in the PCT

- This question asks you to predict what will happen if there is an increase or decrease in sodium/potassium pumps.

Quiz Question #7: Water Reabsorption in the PCT

- This question asks you to predict what will happen if there is an increase in sodium/potassium pumps.

Quiz Question #8: Permeability of Loop of Henle

- This question asks you to rate the impermeability of the ascending and descending loop of Henle to water, sodium ions and chloride ions.

Quiz Question #9: Vasa Recta 1

- This question asks you to determine why there is a movement of water out of the blood and a gain of sodium and chloride ions in the blood as the blood descending in the vasa recta.

** This animation is best viewed in slow motion. You may want to click on the "Settings" button at the bottom of the screen and adjust the animation speed.

Quiz Question #10: Vasa Recta 2

- This question asks you to predict why blood moves sluggishly in the vasa recta.

Quiz Question #11: Vasa Recta 3

- This question asks you to determine why there is a movement of sodium and chloride ions out of the blood and a gain of water in the blood as the blood ascends in the vasa recta.

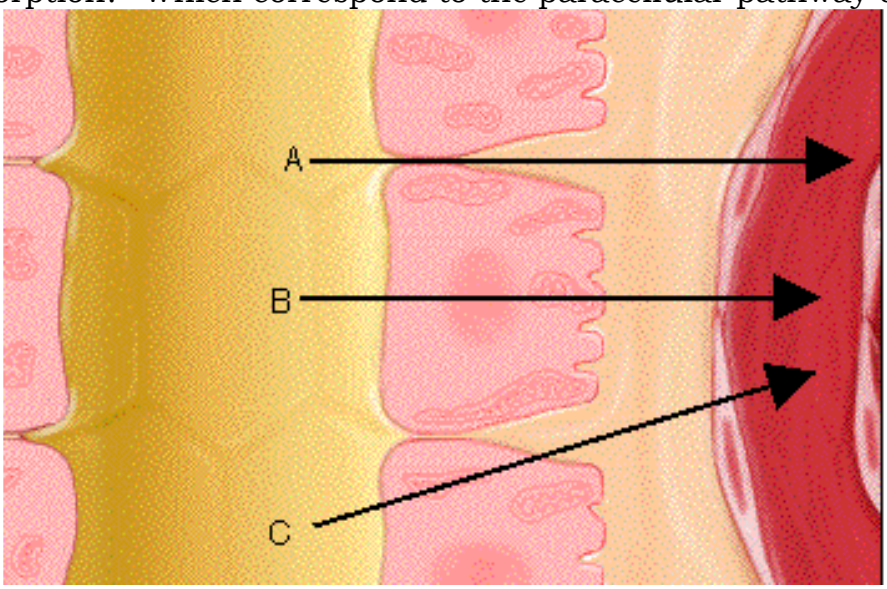
Study Questions on Early Filtrate Processing:

1. (Page 1.) What two renal processes are accomplished by the renal tubules? Briefly review each process.

2. (Page 3.) Which is a more selective process: glomerular filtration or reabsorption? Discuss.

3. (Page 4.) What are the two pathways for reabsorption?

4. (Page 3.) Which arrows below correspond to the transcellular pathway for reabsorption? Which correspond to the paracellular pathway of reabsorption?



5. (Page 4.) Trace the movement of a substance via the transcellular pathway.

6. (Page 4.) Trace the movement of a substance via the paracellular pathway.

7. (Page 4.) Do most solutes use the transcellular or paracellular pathways?

8. (Page 4.) What substances use the paracellular pathway?

9. (Page 5). What is the driving force for glomerular filtration?

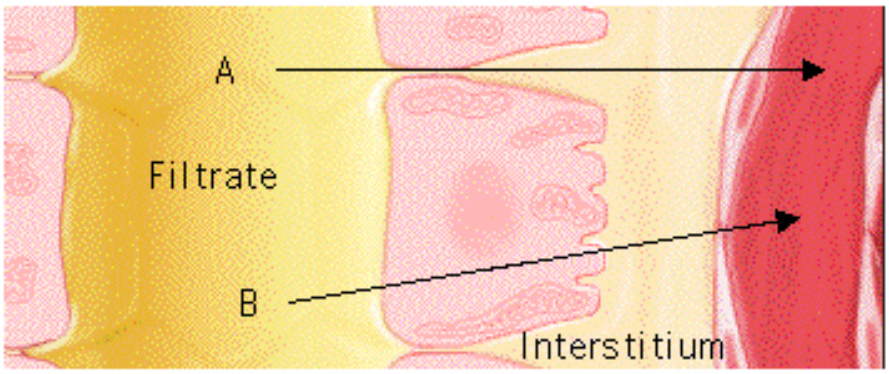
10. (Page 5.) What is the difference between a solution that has a high osmolarity and a solution that has a low osmolarity?

11. (Page 5.) Water tends to move from areas of (select all that apply):
    a. lower water concentration to areas of higher water concentration
    b. higher water concentration to areas of lower water concentration
    c. areas of higher osmolarity to areas of lower osmolarity
    d. areas of lower osmolarity to areas of higher osmolarity

12. (Page 5.) What is the driving force for the reabsorption of water?

13. (Page 5.) If water is to be reabsorbed from the filtrate to the interstitium, which would have to have the higher osmolarity, the filtrate or the interstitium?

14. (Page 5.) What are the two ways that water can diffuse from the filtrate to the interstitium? Classify the two ways using the diagram below:



15. (Page 6.) How can the osmolarity of the interstitium be increased?

16. (Page 7,8.) When sodium ions are transported from the inside of the tubular cells into the interstitium, what happens to the osmolarity of the interstitium? What is the result of changes to the osmolarity of the interstitium?

17. (Page 7,8.) When sodium ions are transported from the inside of the tubular cells into the interstitium, what happens to the movement of ions into the cell? Why does this occur?

18. (Page 9.) Where is the sodium-potassium pump located on tubule cells?

19. (Page 9.) The diagrams to the right represent the function of the sodium potassium pump. Put the diagrams in order, beginning with the binding of sodium to the pump.

20. (Page 9.) Place the following events of the sodium-potassium pump's action in order:

_____ ADP is released and the pump opens to the outside releasing sodium. Two potassiums bind.

_____ ATP is hydrolyzed into ADP and Pi which remains attached to the inner surface of the pump.

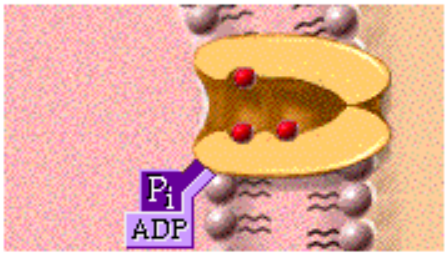
_____ Inside the cell, three sodium's bind to the pump.

_____ ATP binds to the inner surface of the pump.

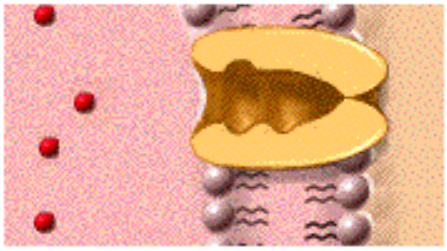
_____ Pi is released from the pump and the pump opens to the inside of the cell, releasing the potassium.

21. (Page 9.) Why is it said that ion pump carries out primary active transport of sodium ions.

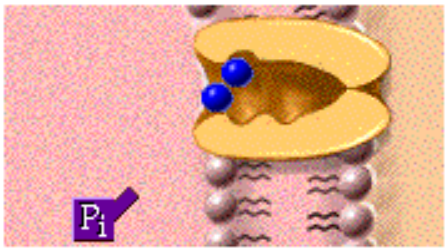
a.



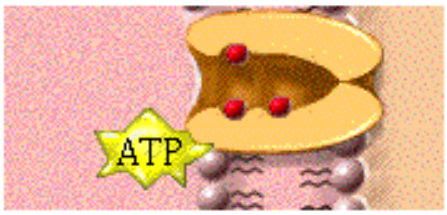
b.



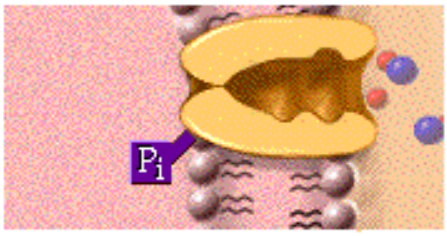
c.



d.



e.



22. (Page 10.) Name three transmembrane proteins found in the basolateral membrane of the PCT.

23. (Page 10.) Explain how the glucose carrier in the basolateral membrane of the PCT works.

24. (Page 10.) What is the purpose of the potassium ion channel in the basolateral membrane of the PCT?

25. (Page 10.) Label the parts of the diagram on p. 10.

26. (Page 11.) Label the diagram on p. 11.

27. (Page 11.) List the names of three transport proteins found on the luminal surface of the cells in the PCT.

28. (Page 11.) a. What is the function of the Sodium-hydrogen Countertransport Molecule on the luminal membrane of the PCT? What does it transport and in what direction? b. Why is its activity dependent on the sodium potassium pump in the basolateral membrane? c. Why is this called countertransport? d. Why is this called secondary active transport?

29. (Page 11.) a. What is the function of the Sodium Channel on the luminal membrane of the PCT? What does it transport and in what direction? b. Why is its activity dependent on the sodium potassium pump in the basolateral membrane?

30. (Page 11.) What is the function of the Sodium-Glucose Cotransport Carrier Molecule on the luminal membrane of the PCT? What does it transport and in what direction? b. Why is its activity dependent on the sodium potassium pump in the basolateral membrane? c. Why is this called cotransport? d. Why is this called secondary active transport?

31. (Page 11.) Define "the transport maximum".

32. (Page 11.) If the volume of a specific solute in the filtrate exceeds the transport maximum, what happens to the excess solute?

33. (Page 12.) Why do diabetics end up with glucose in their urine?

34. (Page 14.) What causes water to diffuse via the paracellular pathway?

35. (Page 14.) Explain solvent drag.

36. (Page 15.) Approximately what percentage of filtrate is reabsorbed in the PCT?

37. (Page 15.) What molecules are usually totally reabsorbed in the PCT?

38. (Page 16.) What is reabsorbed in the thin ascending loop of Henle? What is the driving force for that reabsorption?

39. (Page 16.) Why are sodium and chloride ions not reabsorbed in the thin descending loop of Henle?

40. (Page 16.) What happens to the concentration of the filtrate as it moves down the thin descending loop of Henle?

41. (Page 17.) Label the diagram on p. 17.

42. (Page 17.) What is reabsorbed in the thick ascending loop of Henle and early DCT?

43. (Page 18.) The cells of the ascending limb of the loop of Henle are able to maintain an osmotic difference between these two fluids of approximately 200 milliosmoles. What is this due to?

44. (Page 19.) Label the processes in the diagram on p. 19.

45. (Page 19.) Explain the osmolarity of the interstitium in the medulla.

46. (Page 19. Which of these statements applies to the descending loop of Henle and which applies to the ascending loop of Henle?
    a. The fluid inside the tubule becomes more dilute.
    b. The filtrate concentrates as it moves, because water diffuses into the higher osmolarity interstitium.

47. (Page 20.) Where in the loop of Henle is the filtrate the most concentrated?

48. (Page 20.) The countercurrent theory is called that because of the opposing flow of filtrate within the two limbs of the loop. What flows out of the tubule in the descending loop and what flows out in the ascending loop?

49. (Page 20.) What is the purpose of the countercurrent mechanism in the loop of Henle?

50. (Page 21.) The vasa recta forms hairpin loops. a. In the descending portion of the vasa recta loop which direction do water and ions move? b. In the ascending portion of the vasa recta loop which direction do water and ions move? c. What is the net result of these movements?

51. (Overview.) Fill out this chart with "permeable" or "impermeable".

	Permeability to Water	**Permeability to Na^+ and Cl^- Ions**	**Permeability to Glucose**
Proximal Convoluted Tubule			
Descending Loop of Henle			_____
Ascending Loop of Henle			_____

52. (Overview.) Fill out this chart:

Transport Model							
Substance Transported	Sodium & potassium	Potassium Ions	Glucose	Sodium, potassium, & chloride	Sodium ions	Chloride ions	Sodium & glucose
Membrane Location							
Transport Mechanism							
Transport Method							

53. (Overview.) Fill out this chart with "concentrates", "dilutes", "moves in", or "moves out".

	Descending Loop of Henle	**Ascending Loop of Henle**
Sodium & Chloride Ions		
Water		
Filtrate		

Late Filtrate Processing

Page 1. Introduction

- The final processing of filtrate in the late distal convoluted tubule and collecting ducts comes under direct physiological control.
- In this region, membrane permeabilities and cellular activities are altered in response to the body's need to retain or excrete specific substances.

Page 2. Goals

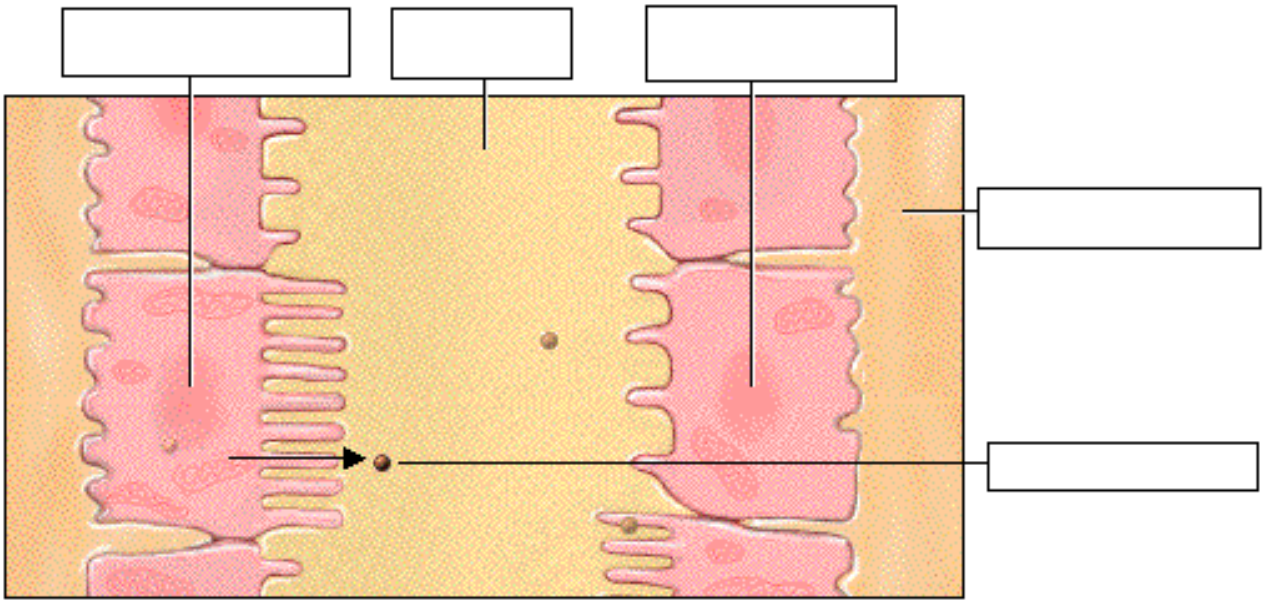
- To understand the role of the hormone aldosterone in the reabsorption of sodium and secretion of potassium.
- To examine the role of the antidiuretic hormone in the concentration of urine.
- To understand the role of the medullary osmotic gradient in the concentration of urine.

Page 3. Late Filtrate Processing: Analogy

- The bulk of reabsorption occurs in the early tubular segments. In these regions the rates of both reabsorption and secretion are relatively constant, because the membrane permeabilities are relatively fixed.
- In the later tubular segments you are about to tour, the membrane permeabilities change in response to changing physiological conditions and hormone levels. This variability provides a mechanism for precisely regulating the final balance of fluid and solutes returned to the blood.
- An analogy for this two-stage process would be to use a steady but unregulated flow to fill a container to almost the level needed--that's early filtrate processing. Then use a precisely regulated flow of water to top off to the exact level--that's late filtrate processing. Bulk filling is analogous to the reabsorption of water and solutes occurring in the early tubular segments. Fine-tuning is analogous to late filtrate processing.

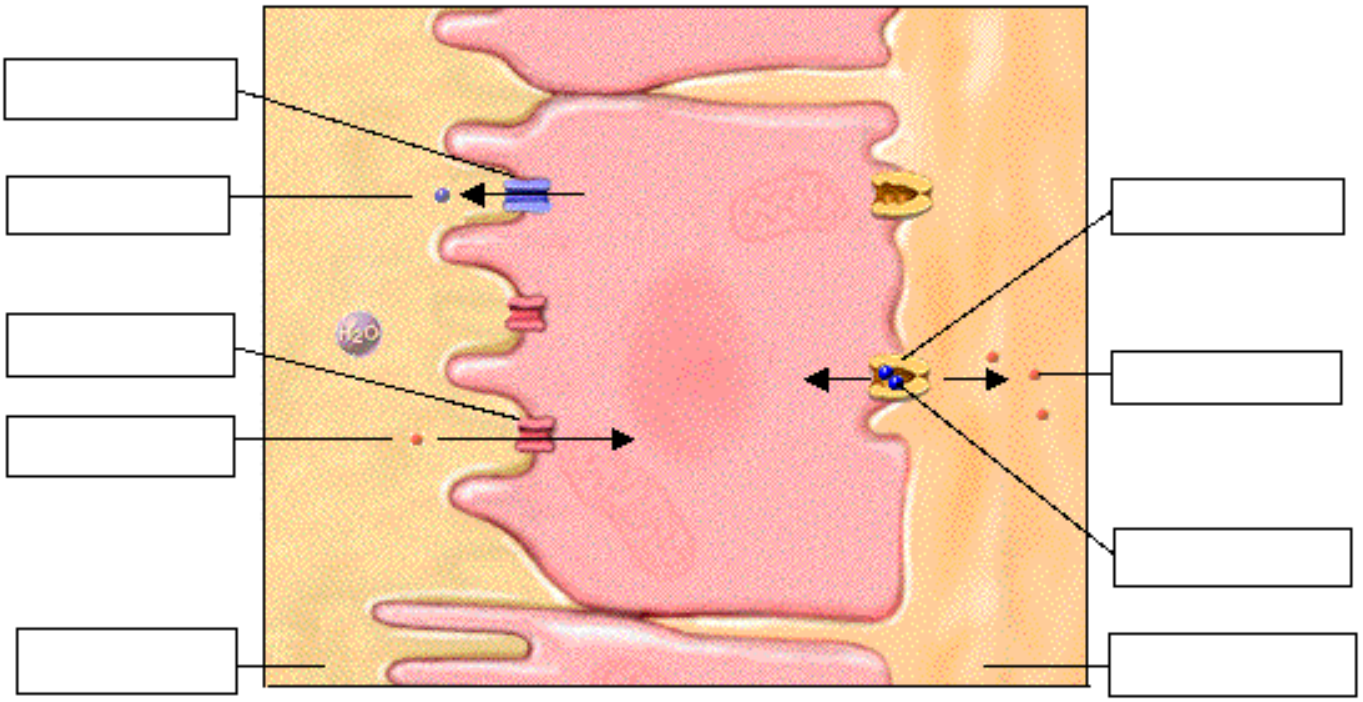
Page 4. Filtrate Processing in the CCD: Hydrogen Ion Secretion

- The epithelium of the collecting ducts consists of two cell types. Each of these cells plays a different role in the final processing of filtrate.
  1. Intercalated cells
     The intercalated cells help to balance the blood pH by secreting hydrogen ions into the filtrate through ATPase pumps in the luminal membrane.
  2. Principal cells
     The principal cells perform hormonally regulated water and sodium reabsorption and potassium secretion.
  - Label this diagram of the two cell types in the late distal convoluted tubule and the collecting ducts:



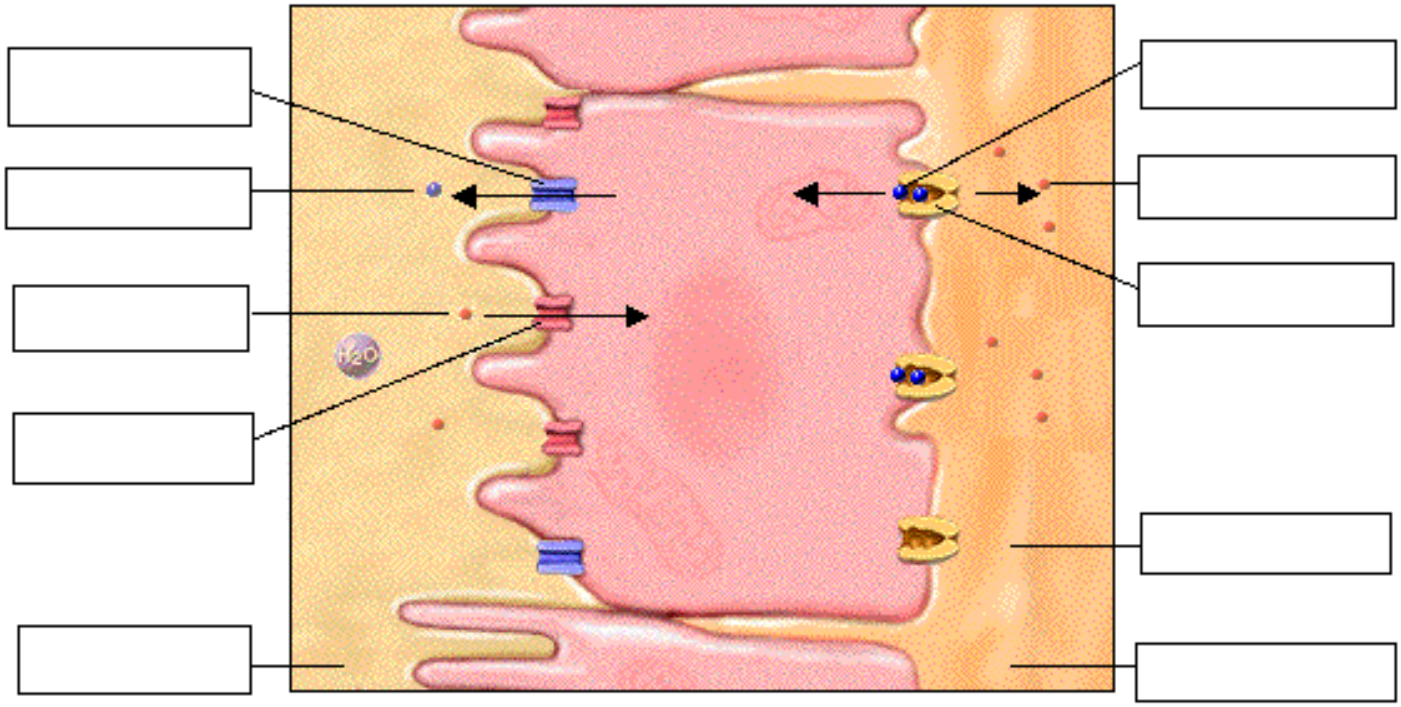
Page 5. Filtrate Processing in the CCD: Role of Aldosterone

- The permeability of the principal cells are permeable to sodium ions and water is controlled by two hormones: aldosterone from the adrenal gland and antidiuretic hormone, or ADH, from the posterior pituitary gland.
- Let's first look at the role of aldosterone, which precisely regulates the final amount of sodium reabsorbed. When levels of sodium and potassium ions in the blood are balanced, aldosterone levels remain low. As a result, there are few sodium-potassium ATPase ion pumps in the basolateral membrane and few sodium and potassium channels in the luminal membrane. Therefore, sodium ion reabsorption and potassium ion secretion are both low.
- Label this diagram to show what happens when levels of sodium and potassium ions in the blood are balanced and aldosterone levels remain low:



- However, a decrease in the level of sodium ions or an increase in potassium ions in the blood will trigger the release of aldosterone.

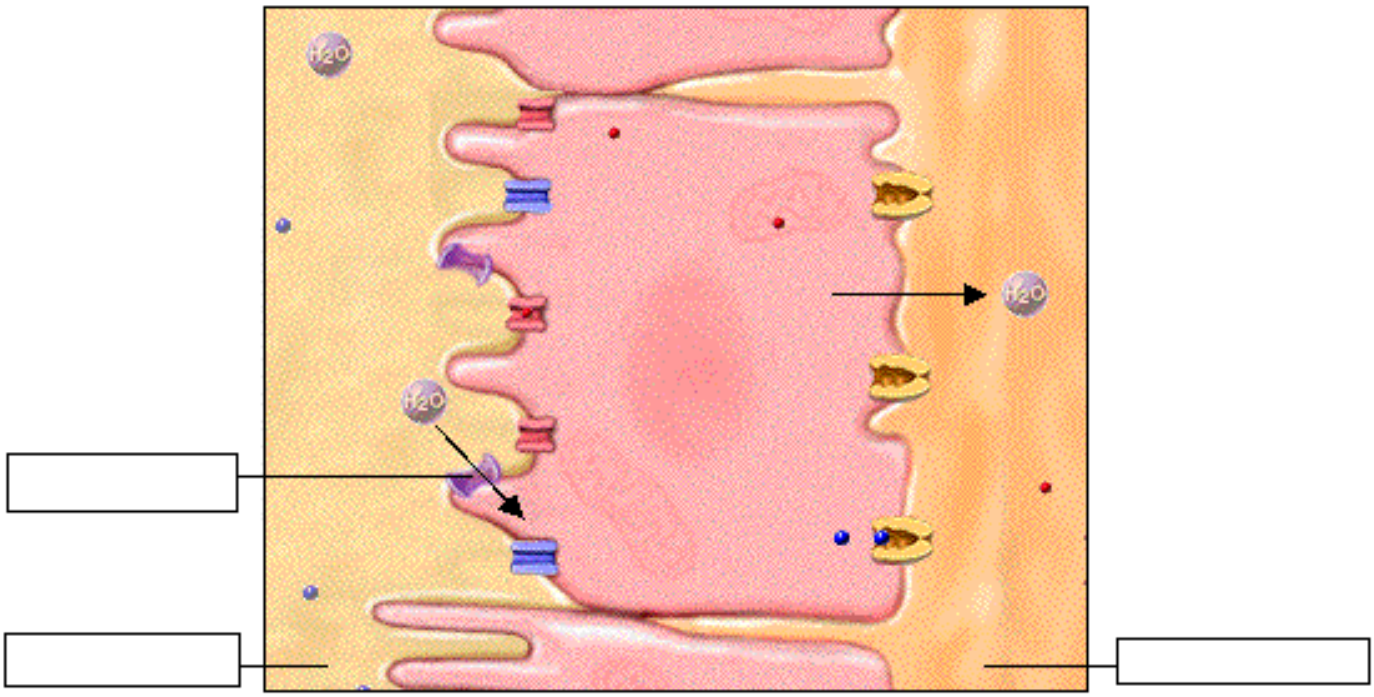
- Label this diagram to show what happens when aldosterone levels are high:



- In response to increased aldosterone, both sodium ion reabsorption and potassium ion secretion increase.
- This occurs because the principal cells increase the number and activity of sodium/potassium pumps in the basolateral membrane. The number of sodium and potassium channels in the luminal membrane is also increased.
- Notice the absence of potassium channels in the basolateral membrane. Potassium ions enter the cell through the basolateral membrane, but instead of diffusing back into the interstitium, they diffuse to the luminal membrane and are secreted into the filtrate.
- The effects of aldosterone are not confined to the collecting duct. It has similar effects on cells of the distal convoluted tubule.
- You should also notice the resulting increase in interstitial osmolarity. Water is not following the solute, because the luminal membrane of the collecting duct is relatively impermeable to water unless it is stimulated by ADH.

Page 6. Filtrate Processing in the CCD: Role of Antidiuretic Hormone

- Aldosterone and antidiuretic hormone act independently to regulate salt and water, but can also work together.
- The cell you see here has been stimulated as yet only by aldosterone, so it is still impermeable to water.
- When stimulated by ADH, principal cells quickly insert luminal water channels, increasing their water permeability.
- Notice that the interstitial osmolarity decreases. When water molecules can diffuse through a membrane, osmolarities on each side of the membrane equilibrate.
- Label this diagram to show what happens when both aldosterone and ADH levels are high:

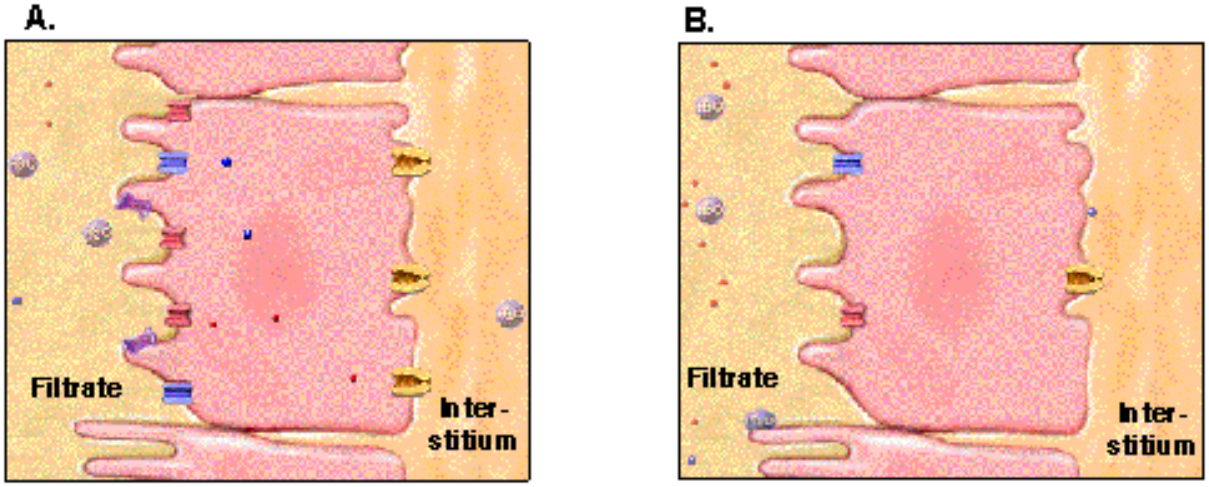


Page 7. Response to Dehydration and Overhydration

- Now let's look at two common conditions to demonstrate how ADH functions in our everyday lives.
- Dehydration:
  - In dehydration, which could be caused by hot weather, perspiration causes the body to lose both water and sodium.
  - In response, ADH is released; it stimulates the kidney to conserve body fluid by increasing reabsorption of water from the filtrate.
  - Therefore, the volume of filtrate entering the medullary collecting duct is reduced, so urine volume decreases.
- Overhydration:
  - Overhydration, which could be caused by drinking several cans of soda or other beverages, triggers a decrease in ADH.
  - As a result, membrane permeability for water and sodium ions decreases, reabsorption slows dramatically, and the volume of filtrate entering the medullary collecting duct increases above the normal level, causing urine volume to increase.
  - High urine volumes also occur when substances containing diuretic chemicals are consumed.
- Circle the appropriate words below for each picture:

Dehydration or Overhydration Dehydration or Overhydration

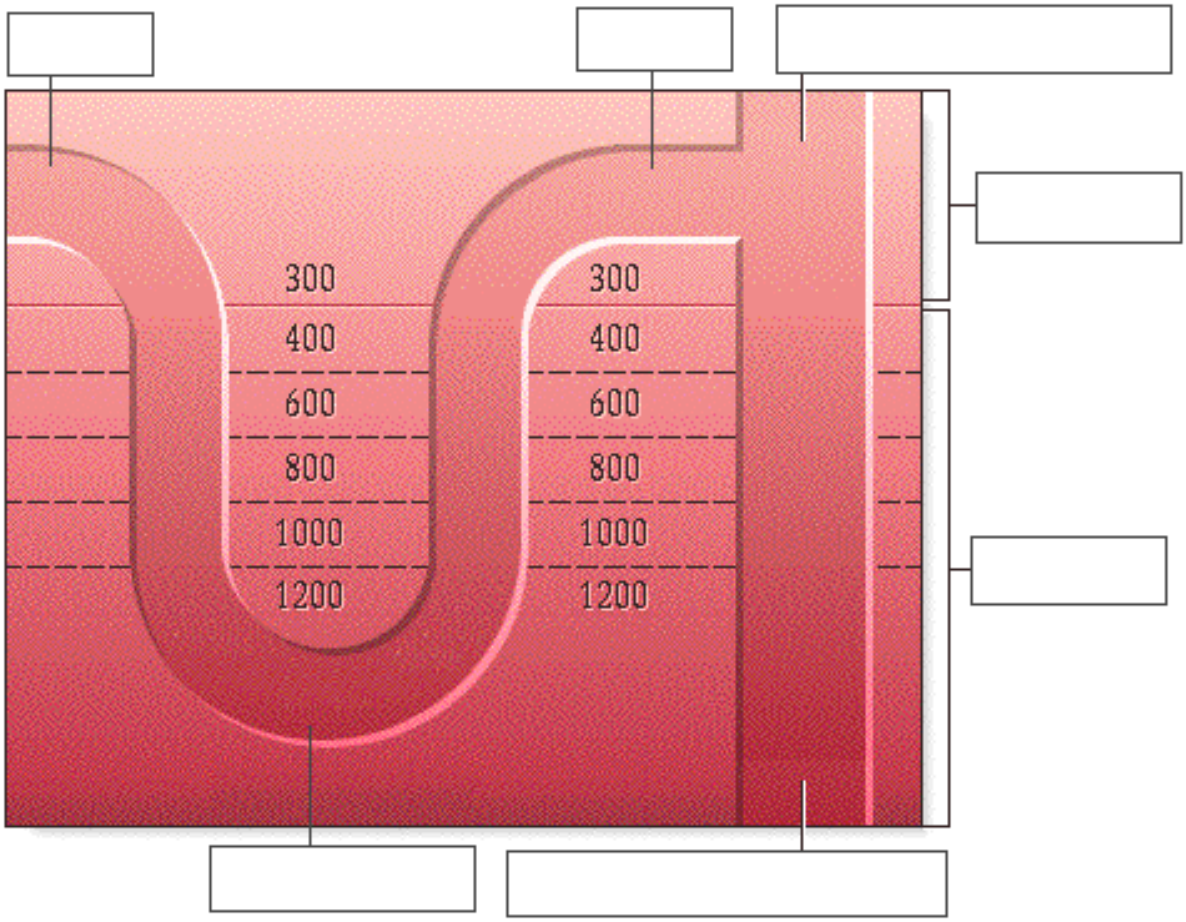
High ADH or Low ADH High ADH or Low ADH



- If you increase plasma volume by drinking fluids, you effectively dilute the sodium content of the extracellular fluids including blood plasma, thus turning down the stimulus for ADH release. If those drinks are caffeinated like coffee or alcoholic like beer, the fluid output may be higher than anticipated because those substances have a diuretic effect. A diuretic is a chemical that increases urine output. For example caffeine promotes vasodilation thus increasing the GFR and alcohol has an effect on release of ADH.

Page 8. Medullary Osmotic Gradient: Review

- We are now ready for the final concentration of the filtrate as it enters the medullary collecting duct.
- Recall from the Early Filtrate Processing topic that the asymmetrical pattern of reabsorption in the ascending and descending loop of Henle created an osmotic gradient in the renal medulla.
- Here again is the schematic medullary gradient. The dark color in the deeper regions of the gradient represents a high solute concentration that gradually changes to the lighter, low solute concentration near the cortex. The solutes forming the gradient are sodium and chloride ions and other substances including urea. We now add osmolarity indicators in milliosmole units and a schematic diagram of the tubules and collecting ducts.
- Label this diagram:



Page 9. Progressive Change in Filtrate Osmolarity

- Using this schematic diagram, let's review how filtrate concentration in the tubules is related to interstitial osmolarity. Watch the changes in the concentration and volume of the filtrate as it passes through the differing osmotic environments of the cortex and medulla.
- Fill out this chart as you proceed:

	Proximal Convoluted Tubule	Descending Loop of Henle	Ascending Loop of Henle	Late Distal Convoluted Tubule and Cortical Collecting Duct
Osmolarity of Filtrate				
Osmolarity if Interstitium				
Permeability to Water				
Permeability to Solutes				
Filtrate Volume				

- **Proximal Convoluted Tubule:**
  - Since the cells of the PCT are highly permeable to both solutes and water, the relative osmolarity of the filtrate remains equal to the 300 milliosmole solute concentration of the interstitium.
  - The cells' high permeability also accounts for a 65% reduction in filtrate volume.
- **Descending Loop of Henle:**
  - Watch the simulated drop of filtrate as it moves down the tube to the bottom of the loop. Notice that the osmolarity of the filtrate increases and the volume decreases. Recall that the cells of this region are permeable to water but not to solute.
  - As the filtrate moves down the tube through regions of higher osmolarity, water diffuses out into the interstitium, reducing the filtrate volume by an additional 15%. The solutes remain behind in the tubule and become more concentrated as the filtrate approaches the bottom of the loop.
- **Ascending Loop of Henle:**
  - The cells of the thick segment of the ascending loop of Henle are permeable to solute but not to water, making them function essentially opposite to the cells of the thin segment of the descending loop.
  - As the concentrated filtrate flows up the ascending loop, the cells actively transport solutes into the interstitium, causing the osmolarity of the filtrate to fall to less than 300 milliosmoles.
  - Because water remains in the tubule, the filtrate volume remains unchanged.
  - The opposing flow and opposite activities of the descending and ascending segments of the loop of Henle is called the countercurrent multiplier mechanism.
- **Cortical Collecting Duct**
  - The osmolarity of the filtrate entering the late DCT and cortical collecting duct can be as low as 100 milliosmoles.
  - Recall that in the cells of this region, the reabsorption of sodium ions and water is regulated by the hormones aldosterone and antidiuretic hormone respectively.
  - In normal hydration conditions, low levels of both hormones promote the reabsorption of sodium ions and water from the filtrate. This maintains the low osmolarity of the filtrate, while reducing its volume by an additional 15%.

Page 10. Urine Concentration: Medullary Collecting Duct

- The last step in the formation of urine occurs as the filtrate passes down the medullary collecting duct.
- Of the 125 milliliters per minute of filtrate that entered the proximal convoluted tubule from the glomerular capsule, 95% has been reabsorbed back into the blood.
- Only about 6 milliliters per minute, or 5%, remains to enter the medullary collecting duct.
- Antidiuretic hormone regulates the final amount of water reabsorbed in the collecting duct, and thus determines the final concentration of urine.

Page 11. Conditions Affecting Final Urine Volume

- The osmotic gradient constructed by the countercurrent multiplier mechanism concentrates the urine by drawing water from the filtrate as it travels through the medullary collecting duct.

- The degree of concentration is regulated by antidiuretic hormone, which controls the water permeability of the duct. ADH levels vary in response to various conditions, including the individual's hydration status.
- Fill in this table as you go through the rest of this page:

	Normal Hydration	**Dehydration**	**Overhydration**
ADH Secretion			
Presence of Water Channels in Medullary Collecting Duct			
Water Permeability			
Urea Permeability			
Interstitial Medullary Osmolarity			
Osmolarity of Urine			

- **Normal Hydration**
  - With normal hydration and levels of ADH, water channels are present in the luminal membranes of these cells, resulting in moderate water permeability.
  - ADH also facilitates the diffusion of urea out of the medullary collecting duct into the interstitium.
  - Although it is considered a nitrogenous waste product, urea is responsible for up to 40% of the medullary interstitial osmolarity. From the interstitium, urea passively re-enters the filtrate in the loop of Henle and re-circulates back to the collecting ducts. It may then again diffuse into the interstitium or pass into the renal pelvis as a component of urine.
  - Notice that, as it descends, the filtrate drop shrinks in volume and darkens slightly as water is lost and solutes are concentrated.
  - The filtrate does not equilibrate with the osmolarity of all medullary regions and is therefore not as concentrated as possible.
  - Normal urine has an osmolarity of about 600 milliosmoles or twice normal body osmolarity.

- **Dehydration**
  - With dehydration, a high level of ADH creates two important changes:
    1. It causes additional luminal water channels to be added to the duct, which increases its permeability to water.
    2. It increases the permeability of the duct to urea, which in turn increases the interstitial osmolarity. This increased osmolarity draws additional water from the filtrate.
  - Therefore, as the filtrate passes through the lumen of the duct, it equilibrates with each regional increase in osmolarity.
  - Notice the decrease in size and darkening color of the filtrate drop as it descends through the duct.

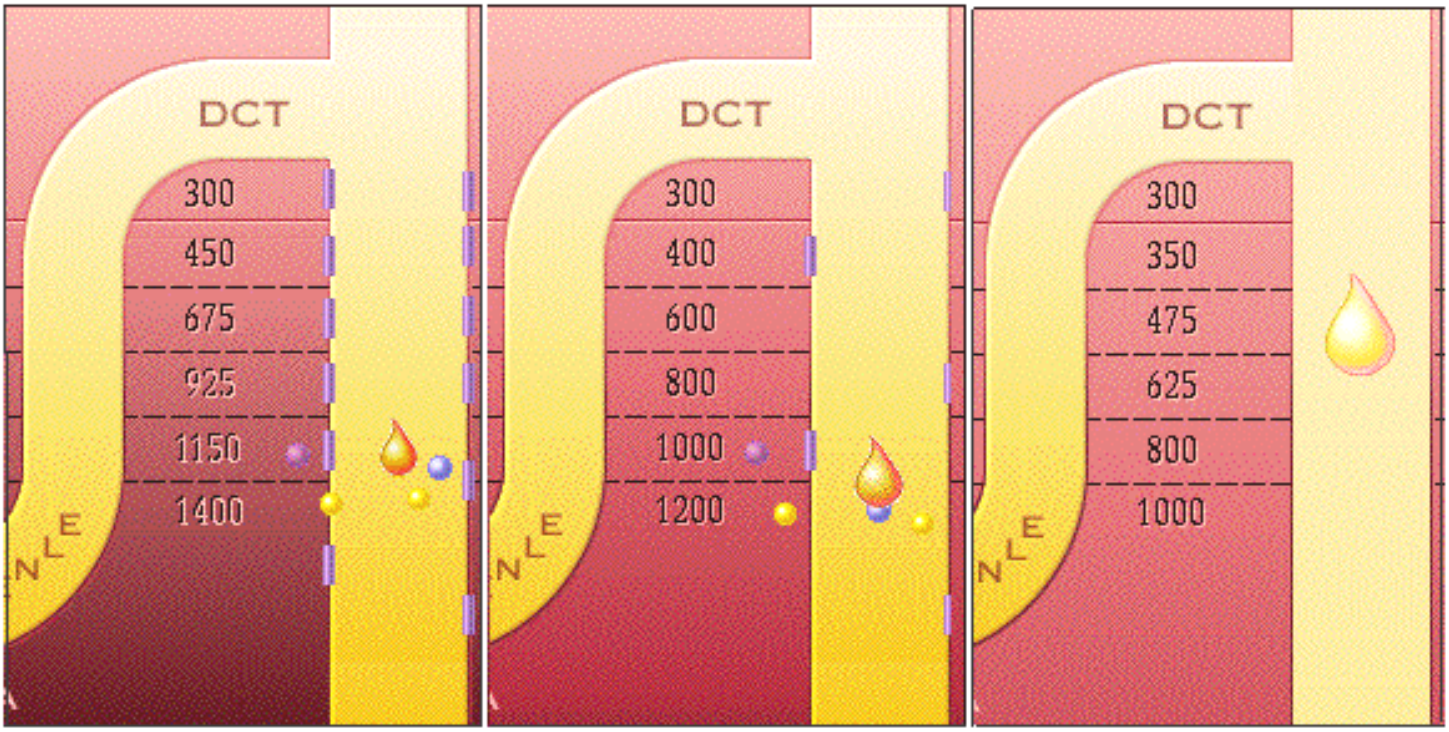
- In severe dehydration conditions, the low volume of urine excreted may be concentrated to about 1400 milliosmoles, or more than four times the osmolarity of normal body fluids.

- **Overhydration**
  - With overhydration, ADH levels are very low or absent, and the duct cells remain relatively impermeable to water and urea.
  - The reduction in urea permeability decreases the medullary interstitial osmotic gradient, reducing the water-drawing power of the interstitium.
  - As the filtrate passes through the lumen of the medullary collecting duct, it does not equilibrate with any regional change in osmolarity and therefore remains unmodified.
  - Notice that the filtrate drop remains the same size and color as it descends through the duct.
  - The final urine, which is dilute and high in volume, may have an osmolarity as low as 100 milliosmoles.
  - Circle the proper state that corresponds to the following diagrams:

dehydrated
normal hydration
overhydration

dehydrated
normal hydration
overhydration

dehydrated
normal hydration
overhydration



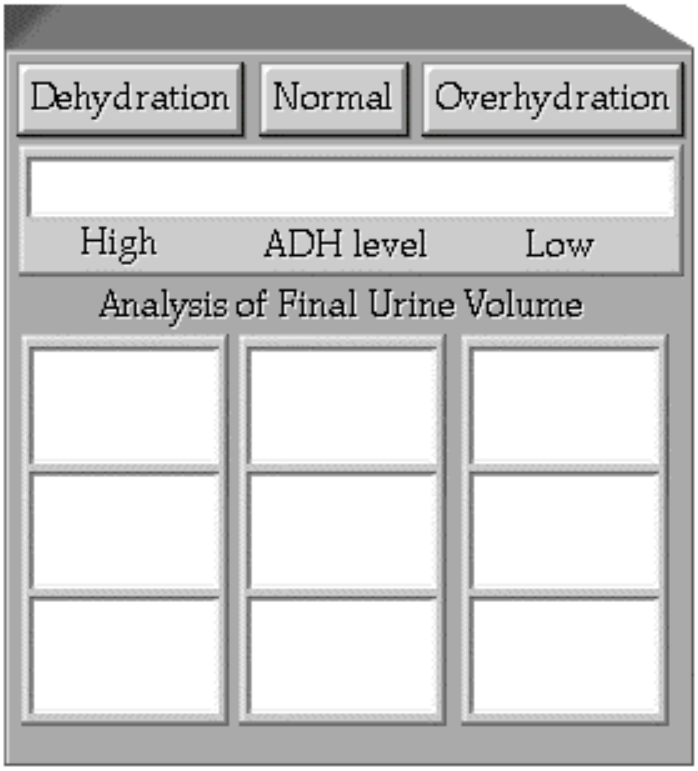
- List two differences between the diagrams above:

1. _____

2. _____

Page 12. Final Urine Volume

- Fill in the chart as you proceed:



- Let's look at the final volume of urine produced per minute and per day for each of the levels of hydration you have just seen.
- Recall that 95% of the water has been reabsorbed from the 125 milliliters per minute of glomerular filtrate produced by the kidney before the filtrate enters the medullary collecting duct.
- Record your data on the chart on the next page.
- With **high levels of antidiuretic hormone**, the approximate final urine volume is 0.2% percent of the filtrate. This is equal to one fourth of a milliliter per minute or 400 milliliters per day. Two conditions in which this might occur would be severe dehydration or blood loss.
- With **normal levels of antidiuretic hormone**, about 99% of the filtrate is reabsorbed into the blood. This leaves about 0.9% or 1.1 milliliters per minute of concentrated urine to continue the passage into the renal pelvis and urinary bladder. This equals about one and one half liters per day.
- With **low levels of antidiuretic hormone**, the approximate final urine volume is 12.5% of the filtrate. This is equal to 16 milliliters per minute or 22.5 liters per day. This situation might be caused by either temporary or chronic conditions. High volumes of dilute urine are temporarily produced after a person drinks either a large volume of fluid or fluids that contain diuretic drugs such as caffeine or alcohol. In a chronic condition called diabetes insipidus, urinary volume may reach extremely high levels, because either antidiuretic hormone is not released by the posterior pituitary or the tubular cells do not bind and respond to this hormone.

Page 13. Summary

- Late filtrate processing includes both reabsorption and secretion.
- Late filtrate processing of sodium, potassium, water, and urea is under direct control of aldosterone and antidiuretic hormone.

- The medullary osmotic gradient and ADH both contribute to final urine concentration.
- In normal conditions, about 99% of the glomerular filtrate is reabsorbed during its passage through the tubules and ducts.

** Now is a good time to go to quiz questions 1-5:
- Click the Quiz button on the left side of the screen..
- Work through quiz questions 1-5.

Notes on Quiz Questions:

Quiz Question #1: Tubular Region Activities
- This question asks you to give the region(s) of the tubule where filtrate become more concentrated.

Quiz Question #2: Tubular Region Activities
- This question asks you to give the region(s) of the tubule where filtrate become more dilute.

Quiz Question #3: Tubular Region Activities
- This question asks you to give the region(s) of the tubule where the volume of filtrate changes.

Quiz Question #4: Dehydration Chain Reaction
- This question asks you to list the proper sequence of events that occurs when dehydration increases or decreases.

Quiz Question #5: Urine Samples
- This question asks you to predict the condition of the patient based on the analysis of the urine sample.

Study Questions on Late Filtrate Processing:

1. (Page 3.) Does most reabsorption occur in the early tubular segments or later tubular segments?

2. (Page 3.) Why does most reabsorption occur in the early tubular segments as opposed to the later tubular segments?

3. (Page 3.) Does fine-tuning of the filtrate occur to a greater extent in the early tubular segments or later tubular segments?

4. (Page 4.) What are the names of the two types of epithelium found in the collecting ducts?

5. (Page 4.) What is the function of the intercalated cells in the collecting ducts?

6. (Page 4.) What is the function of the principal cells in the collecting ducts?

7. (Page 4.) Label the diagram on page 4.

8. (Page 5.) What two hormones control the permeability of principal cells? Where are each of these hormones secreted from?

9. (Page 5.) Label the first diagram on page five that shows what happens when levels of sodium and potassium ions in the blood are balanced and aldosterone levels remain low.

10. (Page 5.) What triggers the release of aldosterone?

11. (Page 5.) What happens to sodium ions and potassium ions in the collecting ducts when there is an increase in aldosterone?

12. (Page 5.) Label the second diagram on page five that shows what happens when aldosterone levels are high.

13. (Page 5.) What happens to membrane transport proteins in the principal cells of the collecting ducts when aldosterone levels are high?

14. (Page 5.) Why does the potassium get secreted, as opposed to being reabsorbed when aldosterone is present in the collecting duct?

15. (Page 5.) Why does the osmolarity of the interstitium increase in the presence of aldosterone and in the absence of ADH?

16. (Page 6.) What is the effect of ADH on principal cells of the collecting ducts?

17. (Page 6.) Label the diagram on p. 6.

18. (Page 6.) What is the effect of ADH on interstitial osmolarity?

19. (Page 7.) What is lost by the body during dehydration due to perspiration?

20. (Page 7.) What hormone is released during dehydration due to perspiration? What is its effect?

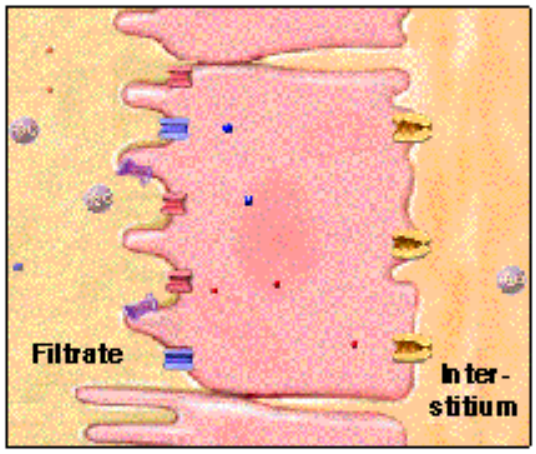
21. (Page 7.) What happens to urine volume as a result of ADH during dehydration?

22. (Page 7.) What happens to the secretion of ADH during overhydration?

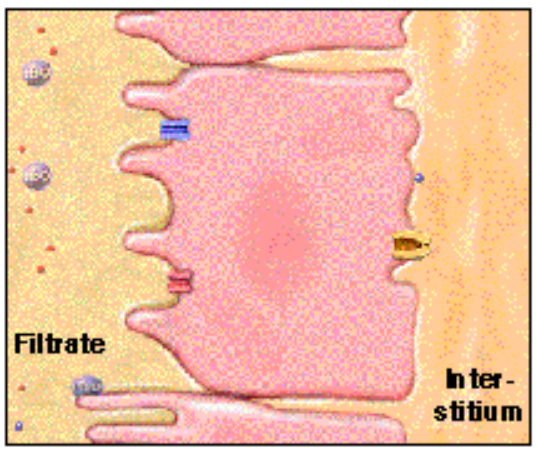
23. (Page 7.) What happens to urine volume in overhydration when ADH levels are low?

24. (Page 7.) Which of the following corresponds to the appearance of the collecting duct when an individual is overhydrated? Which corresponds to dehydration? Explain.

A.



B.



25. (Page 7.) What is a diuretic?

26. (Page 7.) When there is an increase in dehydration, are the following increased or decreased?
    a. Body water _____.
    b. Blood osmolarity _____.
    c. ADH release from the pituitary _____.
    d. Water permeability of the collecting ducts _____.
    e. Water reabsorption _____.
    f. Urine concentration _____.
    g. Urine volume _____.

27. (Page 8.) Label the diagram corresponding to page 8 of the medullary osmotic gradient.

28. (Page 8.) Explain the medullary osmotic gradient.

29. (Page 9.) Fill out the table on page 9.

30. (Page 9.) Under conditions of normal hydration is the filtrate osmolarity in the CCD low or high? Why?

31. (Page 10). Under normal hydration, what percentage volume of fluid is reabsorbed in the following areas of the nephron: a. PCT b. descending Loop of Henle c. ascending Loop of Henle d. cortical collecting duct e. Under normal hydration, what percentage volume of fluid enters the medullary collecting duct?

32. (Page 10). What hormone regulates the final amount of water reabsorbed in the medullary collecting duct?

33. (Page 11.) Fill in the table on p. 11.

34. (Page 11.) Given the interstitial osmolarity diagrams on page 11, chose which corresponds to dehydration, normal hydration, and overhydration.

35. (Page 11.) Given the interstitial osmolarity diagrams on page 11, list two differences between the diagrams.

36. (Page 11.) In the medullary collecting duct, ADH influences the reabsorption of both water and ____.

37. (Page 11.) As urea leaves the medullary collecting duct and travels into the interstitium, what happens to the osmolarity of the interstitium?

38. (Page 11.) What happens to the urea that enters the interstitium?

39. (Page 12.) Place the following figures into the proper column below:
0.2 % of filtrate, 0.9% of filtrate, 12.5% of filtrate
1.25 mL/min, 1.10 mL/min, 16.0 mL/min
0.4 liters/day, 1.5 liters/day, 11.5 liters/day
little or no ADH, moderate ADH, high ADH

	Normal Hydration	Dehydrated	Overhydrated
% of filtrate which becomes urine			
milliliters of urine formed per minute			
liters of urine formed per day			
ADH secreted			

40. (Page 12.) In normal conditions what percentage of the glomerular filtrate is reabsorbed during its passage through the tubules and ducts?

41. (Summary) In which two regions of the tubule does the filtrate become more concentrated?

42. (Summary) In which region of the tubule does the filtrate become more dilute?

43. (Summary) In which region of the tubule does the volume of filtrate change?

44. (Summary) When there is a high level of potassium in the blood, do the following increase or decrease?
    a. adrenal release of aldosterone _____.
    b. sodium/potassium active transport _____.
    c. potassium secretion _____.
    d. sodium excretion _____.
    e. interstitial osmolarity _____.
    f. water reabsorption _____.
    g. urine volume _____.