Urine Formation by the Kidneys: II.

Tubular Processing of the Glomerular Filtrate Reabsorption and Secretion by the Renal Tubules

- As the glomerular filtrate enters the renal tubules, it flows sequentially through the successive parts of the tubule—the proximal tubule, the loop of Henle, the distal tubule, the collecting tubule, and, finally, the collecting duct—before it is excreted as urine.
- Along this course, some substances are selectively reabsorbed from the tubules back into the blood, whereas others are secreted from the blood into the tubular lumen.
- Eventually, the urine that is formed and all the substances in the urine represent the sum of three basic renal processes—glomerular filtration, tubular reabsorption, and tubular secretion— as follows:

Urinary excretion = Glomerular filtration - Tubular reabsorption + Tubular secretion

- For many substances, reabsorption plays a much more important role than does secretion in determining the final urinary excretion rate.
- However, secretion accounts for significant amounts of potassium ions, hydrogen ions, and a few other substances that appear in the urine.
- Tubular Reabsorption Is Selective and Quantitatively Large
- The rate at which each of these substances is filtered is calculated as Filtration = Glomerular filtration rate X Plasma concentration
- <u>This calculation assumes that the substance is freely filtered and not bound to plasma proteins.</u> For example, if plasma glucose concentration is 1 g/L, the amount of glucose filtered each day is about 180 L/day X 1 g/L, or 180 g/day. Because virtually none of the filtered glucose is normally excreted, the rate of glucose reabsorption is also 180 g/day.
- First, the processes of glomerular filtration and tubular reabsorption are quantitatively very large relative to urinary excretion for many substances.
- A small change in glomerular filtration or tubular reabsorption can potentially cause a relatively large change in urinary excretion.
- For example, a 10 per cent decrease in tubular reabsorption, from 178.5 to 160.7 L/day, would increase urine volume from 1.5 to 19.3 L/day (almost a 13-fold increase) if the glomerular filtration rate (GFR) remained constant.
- However, changes in tubular reabsorption and glomerular filtration are closely coordinated, so that large fluctuations in urinary excretion are avoided.
- Unlike glomerular filtration, which is relatively nonselective (that is, essentially all solutes in the plasma are filtered except the plasma proteins or substances bound to them), tubular reabsorption is highly selective.
- Some substances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so that the urinary excretion rate is essentially zero.
- Many of the ions in the plasma, such as sodium, chloride, and bicarbonate, are also highly reabsorbed, but their rates of reabsorption and urinary excretion are variable, depending on the needs of the body.
- Certain waste products, such as urea and creatinine, conversely, are poorly reabsorbed from the tubules and excreted in relatively large amounts.

• By controlling the rate at which they reabsorb different substances, the kidneys regulate the excretion of solutes independently of one another, a capability that allows precise control of the composition of body fluids.

Tubular Reabsorption Includes Passive and Active Mechanisms

For a substance to be reabsorbed, it must first be transported

- (1) across the tubular epithelial membranes into the renal interstitial fluid
- (2) through the peritubular capillary membrane back into the blood
- Reabsorption of water and solutes includes a series of transport steps.
- Reabsorption across the tubular epithelium into the interstitial fluid includes active or passive transport.
- For water and solutes, they can be transported either through the cell membranes themselves (transcellular route) or through the junctional spaces between the cells (para cellular route).
- After absorption across the tubular epithelial cells into the interstitial fluid, water and solutes are transported the rest of the way through the peritubular capillary walls into the blood by **ultrafiltration (bulk flow)** that is mediated by hydrostatic and colloid osmotic forces.
- The peritubular capillaries function very much like the venous ends of most other capillaries because there is a net reabsorptive force that moves the fluid and solutes from the interstitium into the blood.

• Active Transport

Active transport can move a solute against an electrochemical gradient and requires energy derived from metabolism.

- 1. Active Transport: A Transport that is coupled directly to an energy source, such as the hydrolysis of adenosine triphosphate (ATP)
 - A good example of this is the sodium-potassium ATPase pump that functions throughout most parts of the renal tubule.
- 2. Passive Transport: A Transport that is coupled indirectly to an energy source, such as that due to an ion gradient, is referred to as secondary active transport.
 - Reabsorption of glucose by the renal tubule is an example of secondary active transport.
 - Solutes can be reabsorbed by active and/or passive mechanisms by the tubule, water is always reabsorbed by a passive
 - Reabsorption of filtered water and solutes occurs from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood.
 - Solutes are transported through the cells (transcellular route) by passive diffusion or active transport, or between the cells (paracellular route) by diffusion.
 - Water is transported through the cells and between the tubular cells by **osmosis** which is a (nonactive) physical mechanism called osmosis, which means water diffusion from a region of low solute concentration (high water concentration) to one of high solute concentration (low water concentration).
 - Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by **ultrafiltration (bulk flow).**

• Solutes Can Be Transported Through Epithelial Cells or Between Cells.

Renal tubular cells, like other epithelial cells, are held together by tight junctions.

- Lateral intercellular spaces lie behind the tight junctions and separate the epithelial cells of the tubule.
- Solutes can be reabsorbed or secreted across the cells by way of the transcellular pathway or between the cells by moving across the tight junctions and intercellular spaces by way of the paracellular pathway.
- Sodium is a substance that moves through both routes, although most of the sodium is transported through the transcellular pathway.
- In some nephron segments, especially the proximal tubule, water is also reabsorbed across the paracellular pathway, and substances dissolved in the water, especially potassium, magnesium, and chloride ions, are carried with the reabsorbed fluid paracellularly.
- **Primary Active Transport Through the Tubular Membrane Is Linked to Hydrolysis of ATP.** The special importance of primary active transport is that it can move solutes against an electrochemical gradient.
- The energy for this active transport comes from the hydrolysis of ATP by way of membranebound ATPase; the ATPase is also a component of the carrier mechanism that binds and moves solutes across the cell membranes.
- The primary active transporters that are known include sodium-potassium ATPase, hydrogen ATPase, hydrogen potassium ATPase, and calcium ATPase.
- A good example of a primary active transport system is the reabsorption of sodium ions across the proximal tubular membrane,
- On the basolateral sides of the tubular epithelial cell, the cell membrane has an extensive sodium-potassium ATPase system that hydrolyzes ATP and uses the released energy to transport sodium ions out of the cell into the interstitium.
- At the same time, potassium is transported from the interstitium to the inside of the cell. The operation of this ion pump maintains low intracellular sodium and high intracellular potassium concentrations and creates a net negative charge of about -70 millivolts within the cell.
- This pumping of sodium out of the cell across the basolateral membrane of the cell favors passive diffusion of sodium across the luminal membrane of the cell, from the tubular lumen into the cell, for two reasons:

(1) There is a concentration gradient favoring sodium diffusion into the cell because intracellular sodium concentration is low (12 mEq/L) and tubular fluid sodium concentration is high (140 mEq/L).

(2) The negative, -70-millivolt, intracellular potential attracts the positive sodium ions from the tubular lumen into the cell.

- Active reabsorption of sodium by sodium potassium ATPase occurs in most parts of the tubule. In certain parts of the nephron, there are additional provisions for moving large amounts of sodium into the cell.
- In the proximal tubule, there is an extensive brush border on the luminal side of the membrane (the side that faces the tubular lumen) that multiplies the surface area about 20-fold.

- There are also sodium carrier proteins that bind sodium ions on the luminal surface of the membrane and release them inside the cell, providing facilitated diffusion of sodium through the membrane into the cell.
- These sodium carrier proteins are also important for secondary active transport of other substances, such as glucose and amino acids, as discussed later
- In Summary: The net reabsorption of sodium ions from the tubular lumen back into the blood involves at least three steps:

1. Sodium diffuses across the luminal membrane (also called the apical membrane) into the cell down an electrochemical gradient established by the sodium-potassium ATPase pump on the basolateral side of the membrane.

2. Sodium is transported across the basolateral membrane against an electrochemical gradient by the sodium-potassium ATPase pump.

3. Sodium, water, and other substances are reabsorbed from the interstitial fluid into the peritubular capillaries by ultrafiltration, a passive process driven by the hydrostatic and colloid osmotic pressure gradients.

Secondary Active Reabsorption Through the Tubular Membrane.

- In secondary active transport, two or more substances interact with a specific membrane protein (a carrier molecule) and are transported together across the membrane.
- As one of the substances (for instance, sodium) diffuses down its electrochemical gradient, the energy released is used to drive another substance (for instance, glucose) against its electrochemical gradient.
- Secondary active transport does not require energy directly from ATP or from other high energy phosphate sources. Rather, the direct source of the energy is that liberated by the simultaneous facilitated diffusion of another transported substance down its own electrochemical gradient.
- In both instances, a specific carrier protein in the brush border combines with a sodium ion and an amino acid or a glucose molecule at the same time.
- These transport mechanisms are so efficient that they remove almost all the glucose and amino acids from the tubular lumen.
- After entry into the cell, glucose and amino acids exit across the basolateral membranes by facilitated diffusion, driven by the high glucose and amino acid concentrations in the cell.
- Although transport of glucose against a chemical gradient does not directly use ATP, the reabsorption of glucose depends on energy expended by the primary active sodium-potassium ATPase pump in the basolateral membrane.
- Because of the activity of this pump, an electrochemical gradient for facilitated diffusion of sodium across the luminal membrane is maintained, and it is this downhill diffusion of sodium to the interior of the cell that provides the energy for the simultaneous uphill transport of glucose across the luminal membrane.
- Reabsorption of glucose is referred to as "secondary active transport" because glucose itself is reabsorbed uphill against a chemical gradient, but it is "secondary" to primary active trans port of sodium.
- Another important point is that a substance is said to undergo "active" transport when at least one of the steps in the reabsorption involves primary or secondary active transport, even though other steps in the reabsorption process may be passive.

• For glucose reabsorption, secondary active transport occurs at the luminal membrane, but passive facilitated diffusion occurs at the basolateral membrane, and passive uptake by bulk flow occurs at the peritubular capillaries.

Secondary Active Secretion into the Tubules.

Some substances are secreted into the tubules by secondary active transport. This often involves counter-transport of the substance with sodium ions.

- In counter transport, the energy liberated from the downhill movement of one of the substances (for example, sodium ions) enables uphill movement of a second substance in the opposite direction.
- One example of counter-transport is the active secretion of hydrogen ions coupled to sodium reabsorption in the luminal membrane of the proximal tubule.
- In this case, sodium entry into the cell is coupled with hydrogen extrusion from the cell by sodium-hydrogen counter-transport.
- As sodium is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen.
- **Pinocytosis—An Active Transport Mechanism for Reabsorption of Proteins.** Some parts of the tubule, especially the proximal tubule, reabsorb large molecules such as proteins by pinocytosis.
- In this process, the protein attaches to the brush border of the luminal membrane, and this portion of the membrane then invaginates to the interior of the cell until it is completely pinched off and a vesicle is formed containing the protein.
- Once inside the cell, the protein is digested into its constituent amino acids, which are reabsorbed through the basolateral membrane into the interstitial fluid.
- Because pinocytosis requires energy, it is considered a form of active transport.

Transport Maximum for Substances That Are Actively Reabsorbed.

For most substances that are actively reabsorbed or secreted, there is a limit to the rate at which the solute can be transported, often referred to as the transport maximum.

- This limit is due to saturation of the specific transport systems involved when the amount of solute delivered to the tubule (referred to as tubular load) exceeds the capacity of the carrier proteins and specific enzymes involved in the transport process.
- A good example is the glucose transport system in the proximal tubule
- Normally, measurable glucose does not appear in the urine because essentially all the filtered glucose is reabsorbed in the proximal tubule. However, when the filtered load exceeds the capability of the tubules to reabsorb glucose, urinary excretion of glucose does occur.
- In the adult human, the transport maximum for glucose averages about 375 mg/min, whereas the filtered load of glucose is only about 125 mg/min (GFR X plasma glucose = 125 ml/min X 1 mg/ml).
- With large increases in GFR and/or plasma glucose concentration that increase the filtered load of glucose above 375 mg/ min, the excess glucose filtered is not reabsorbed and passes into the urine.
- Note that when the plasma glucose concentration is 100 mg/100 mL and the filtered load is at its normal level, 125 mg/min, there is no loss of glucose in the urine.

- However, when the plasma concentration of glucose rises above about 200 mg/100 ml, increasing the filtered load to about 250 mg/min, a small amount of glucose begins to appear in the urine.
- The point (where <u>some nephrons</u> reached their transport max.) is termed the **threshold** for glucose.
- Note that this appearance of glucose in the urine (at the threshold) occurs before the transport maximum is reached.
- One reason for the difference between threshold and transport maximum is that not all nephrons have the same transport maximum for glucose, and some of the nephrons excrete glucose before others have reached their transport maximum.
- The overall transport maximum for the kidneys, which is normally about 375 mg/min, is reached when all nephrons have reached their maximal capacity to reabsorb glucose.
- The plasma glucose of a healthy person almost never becomes high enough to cause excretion of glucose in the urine, even after eating a meal.
- **Clinical Perspective**: In uncontrolled diabetes mellitus, plasma glucose may rise to high levels, causing the filtered load of glucose to exceed the transport maximum and resulting in urinary glucose excretion.
- Transport maximums for substances actively reabsorbed by the tubules are as follows: Substance Transport Maximum for reabsorbed substances: Glucose 375 mg/min, Phosphate 0.10 mM/min, Sulfate 0.06 mM/min, Amino acids 1.5 mM/min, Urate 15 mg/min, Lactate 75 mg/min, Plasma protein 30 mg/min,
- Transport Maximums for Substances That Are Actively Secreted. Substances that are actively secreted also exhibit transport maximums as follows: Creatinine 16 mg/min, Para-aminohippuric acid PAH 80 mg/min,
- Substances That Are Actively Transported but Do Not Exhibit a Transport Maximum. The reason that actively transported solutes often exhibit a transport maximum is that the transport carrier system becomes saturated as the tubular load increases.
- **Gradient-time transport** : The rate of transport depends on the electrochemical gradient and the time that the substance is in the tubule, which in turn depends on the tubular flow rate.
 - 1. Substances that are passively reabsorbed do not demonstrate a transport maximum because their rate of transport is determined by other factors, such as
 - (1) the electrochemical gradient for diffusion of the substance across the membrane,
 - (2) the permeability of the membrane for the substance
 - (3) the time that the fluid containing the substance remains within the tubule.
 - 2. Some actively transported substances also have characteristics of gradient-time transport. An example is sodium reabsorption in the proximal tubule.
- The main reason that sodium transport in the proximal tubule does not exhibit a transport maximum is that other factors limit the reabsorption rate besides the maximum rate of active transport.
 - 1. In the proximal tubules, the maximum transport capacity of the basolateral sodiumpotassium ATPase pump is usually far greater than the actual rate of net sodium reabsorption
 - 2. Sodium transport in the proximal tubules obeys mainly gradient- time transport principles rather than tubular maximum transport characteristics. Because Significant

amount of sodium transported out of the cell leaks back into the tubular lumen through the epithelial tight junctions. The rate of back leak occurs depends on

- (1) the permeability of the tight junctions and
- (2) the interstitial physical forces, which determine the rate of bulk flow reabsorption from the interstitial fluid into the peritubular capillaries.
- The greater the concentration of sodium in the proximal tubules, the greater its reabsorption rate.
- The slower the flow rate of tubular fluid, the greater the percentage of sodium that can be reabsorbed from the proximal tubules.

In Contrary: In the more distal parts of the nephron, the epithelial cells have much tighter junctions and transport much smaller amounts of sodium. In these segments, sodium reabsorption exhibits a transport maximum similar to that for other actively transported substances. This transport maximum can be increased in response to certain hormones, such as aldosterone.

Passive Water Reabsorption by Osmosis Is Coupled Mainly to Sodium Reabsorption

- When solutes are transported out of the tubule by either primary or secondary active transport, their concentrations tend to decrease inside the tubule while increasing in the renal interstitium.
- This creates a concentration difference that causes osmosis of water in the same direction that the solutes are transported, from the tubular lumen to the renal interstitium.
- Some parts of the renal tubule, especially the proximal tubule, are highly permeable to water, and water reabsorption occurs so rapidly leaving as result only a small concentration gradient for solutes across the tubular membrane.
- A large part of the osmotic flow of water occurs through the so-called tight junctions between the epithelial cells as well as through the cells themselves where junctions between the cells are not as tight as their name would imply, and they allow significant diffusion of water and small ions as in proximal tubules, which have a high permeability for water and a smaller but significant permeability to most ions, such as sodium, chloride, potassium, calcium, and magnesium.
- As water moves across the tight junctions by osmosis, it can also carry with it some of the solutes, a process referred to as solvent drag.
- changes in sodium reabsorption significantly influence the reabsorption of water and many other solutes because the reabsorption of water, organic solutes, and ions is coupled to sodium reabsorption.
- In the more distal parts of the nephron, beginning in the loop of Henle and extending through the collecting tubule, the tight junctions become far less permeable to water and solutes, and the epithelial cells also have a greatly decreased membrane surface area thus, less water osmosis.
- Antidiuretic hormone (ADH) greatly increases the water permeability in the distal and collecting tubules. Thus, water movement across the tubular epithelium can occur only if the membrane is permeable to water, no matter how large the osmotic gradient.

- In the proximal tubule, the water permeability is always high, and water is reabsorbed as rapidly as the solutes.
- In the ascending loop of Henle, water permeability is always low, so that almost no water is reabsorbed, despite a large osmotic gradient.
- Water permeability in the last parts of the tubules—the distal tubules, collecting tubules, and collecting ducts—can be high or low, depending on the presence or absence of ADH.

Reabsorption of Chloride, Urea, and Other Solutes by Passive Diffusion

• Chloride

- Because of sodium reabsorption, negative ions such as chloride are transported along with sodium because of electrical potentials that was built after transport of positively charged sodium ions out of the lumen leaving the inside of the lumen negatively charged, compared with the interstitial fluid causing chloride ions to diffuse passively through the paracellular pathway.
- Additional reabsorption of chloride ions occurs because of a chloride concentration gradient that develops when water is reabsorbed from the tubule by osmosis, thereby concentrating the chloride ions in the tubular lumen.
- Thus, the active reabsorption of sodium is closely coupled to the passive reabsorption of chloride by way of an electrical potential and a chloride concentration gradient.
- The most important of the secondary active transport processes for chloride reabsorption involves co-transport of chloride with sodium across the luminal membrane.
- Urea
- Urea is also passively reabsorbed from the tubule, but to a much lesser extent than chloride ions.
- As water is reabsorbed from the tubules (by osmosis coupled to sodium reabsorption), urea concentration in the tubular lumen increases creating a concentration gradient favoring the reabsorption of urea.
- However, urea does not permeate the tubule as readily as water. In some parts of the nephron, especially the inner medullary collecting duct, passive urea reabsorption is facilitated by specific urea transporters.
- One half of the urea that is filtered by the glomerular capillaries is reabsorbed from the tubules.
- The remainder of the urea passes into the urine, allowing the kidneys to excrete large amounts of this waste product of metabolism.
- Creatinine,
- Creatinine is larger molecule than urea and is essentially impermeant to the tubular membrane, thus, almost none of the creatinine that is filtered is reabsorbed, so that almost all the creatinine filtered by the glomerulus is excreted in the urine.
- Reabsorption and Secretion Along Different Parts of the Nephron Proximal Tubular Reabsorption
- Normally, about 65 per cent of the filtered load of sodium and water and a slightly lower percentage of filtered chloride are reabsorbed by the proximal tubule before the filtrate reaches the loops of Henle. (can be increased or decreased in different physiologic conditions)

- Proximal Tubules Have a High Capacity for Active and Passive Reabsorption due to its special cellular characteristics,
- The proximal tubule epithelial cells are highly metabolic and have large numbers of mitochondria to support potent active transport processes.
- The proximal tubular cells have an extensive brush border on the luminal (apical) side of the membrane as well as an extensive labyrinth of intercellular and basal channels, all of which together provide an extensive membrane surface area on the luminal and basolateral sides of the epithelium for rapid transport of sodium ions and other substances.
- The extensive membrane surface of the epithelial brush border is also loaded with protein carrier molecules that transport a large fraction of the sodium ions across the luminal membrane linked by way of the cotransport mechanism with multiple organic nutrients such as amino acids and glucose.
- The remainder of the sodium is transported from the tubular lumen into the cell by countertransport mechanisms, which reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen ions.
- The secretion of hydrogen ions into the tubular lumen is an important step in the removal of bicarbonate ions from the tubule (by combining H+ with the HCO3 _ to form H2CO3, which then dissociates into H2O and CO2).
- Although the sodium-potassium ATPase pump provides the major force for reabsorption of sodium, chloride, and water throughout the proximal tubule, there are some differences in the mechanisms by which sodium and chloride are transported through the luminal side of the early and late portions of the proximal tubular membrane.
- In the first half of the proximal tubule, sodium is reabsorbed by co-transport along with glucose, amino acids, and other solutes.
- In the second half of the proximal tubule, little glucose and amino acids remain to be reabsorbed. Sodium is now reabsorbed mainly with chloride ions. The second half of the proximal tubule has a relatively high concentration of chloride (around 140 mEq/L) compared with the early proximal tubule (about 105 mEq/L) because in the early proximal tubule when sodium is reabsorbed, alongside, most glucose, bicarbonate, and organic ions were transported, leaving higher concentration of chloride.
- The higher chloride concentration in the second half favors the diffusion of this ion from the tubule lumen through the intercellular junctions into the renal interstitial fluid.
- Concentrations of Solutes Along the Proximal Tubule.

Although the amount of sodium in the tubular fluid decreases markedly along the proximal tubule, the concentration of sodium (and the total osmolarity) remains relatively constant because water permeability of the proximal tubules is so great that water reabsorption keeps pace with sodium reabsorption.

- Certain organic solutes, such as glucose, amino acids, and bicarbonate, are much more avidly reabsorbed than water, so that their concentrations decrease markedly along the length of the proximal tubule.
- Other organic solutes that are less permeant and not actively reabsorbed, such as creatinine, increase their concentration along the proximal tubule.
- The total solute concentration, as reflected by osmolarity, remains essentially the same all along the proximal tubule because of the extremely high permeability of this part of the nephron to water.
- Secretion of Organic Acids and Bases by the Proximal Tubule.

The proximal tubule is also an important site for secretion of organic acids and bases such as bile salts, oxalate, urate, and catecholamines.

- Many of these substances are metabolites and must be eliminated from the body. The following factors combined contribute to rapid excretion in the urine.
 - 1. The secretion of these substances into the proximal tubule
 - 2. filtration into the proximal tubule by the glomerular capillaries
 - 3. Poor reabsorption by the tubules,
- In addition to the waste products of metabolism, the kidneys secrete many potentially harmful drugs or toxins directly through the tubular cells into the tubules and rapidly clear these substances from the blood.
- In the case of certain drugs, such as penicillin and salicylates, the rapid clearance by the kidneys creates a problem in maintaining a therapeutically effective drug concentration.
- Another compound that is rapidly secreted by the proximal tubule is para-aminohippuric acid (PAH). PAH is secreted so rapidly that the average person can clear about 90 per cent of the PAH from the plasma flowing through the kidneys and excrete it in the urine.
- The rate of PAH clearance as result can be used to estimate the renal plasma flow
- Henle consists of three functionally distinct segments:
- The thin descending segment,
- The thin ascending segment,
- The thick ascending segment.
- The thin descending and thin ascending segments, as their names imply, have thin epithelial membranes with no brush borders, few mitochondria, and minimal levels of metabolic activity.
- The descending part of the thin segment is highly permeable to water and moderately permeable to most solutes, including urea and sodium. The function of this nephron segment is mainly to allow simple diffusion of substances through its walls. About 20 per cent of the filtered water is reabsorbed in the loop of Henle, and almost all of this occurs in the thin descending limb.
- The ascending limb, including both the thin and the thick portions, is virtually impermeable to water, a characteristic that is important for concentrating the urine.

- The thick segment of the loop of Henle, which begins about halfway up the ascending limb, has thick epithelial cells that have high metabolic activity and are capable of active reabsorption of sodium, chloride, and potassium.
- About 25 per cent of the filtered loads of sodium, chloride, and potassium are reabsorbed in the loop of Henle, mostly in the thick ascending limb. Considerable amounts of other ions, such as calcium, bicarbonate, and magnesium, are also reabsorbed in the thick ascending loop of Henle.
- The thin segment of the ascending limb has a much lower reabsorptive capacity than the thick segment and the thin descending limb does not reabsorb significant amounts of any of these solutes.
- An important component of solute reabsorption in the thick ascending limb is the sodiumpotassium ATPase pump in the epithelial cell basolateral membranes.
- As in the proximal tubule, the reabsorption of other solutes in the thick segment of the ascending loop of Henle is closely linked to the reabsorptive capability of the sodium-potassium ATPase pump, which maintains a low intracellular sodium concentration.
- The low intracellular sodium concentration in turn provides a favorable gradient for movement of sodium from the tubular fluid into the cell. In the thick ascending loop, movement of sodium across the luminal membrane is mediated primarily by a 1-sodium, 2-chloride, 1-potassium co-transporter.
- This co-transport protein carrier in the luminal membrane uses the potential energy released by downhill diffusion of sodium into the cell to drive the reabsorption of potassium into the cell against a concentration gradient.
- The thick ascending limb of the loop of Henle is the site of action of the powerful "loop" diuretics furosemide, ethacrynic acid, and bumetanide, all of which inhibit the action of the sodium 2-chloride, potassium co-transporter.
- There is also significant paracellular reabsorption of cations, such as Mg++, Ca++, Na+, and K+, in the thick ascending limb owing to the slight positive charge of the tubular lumen relative to the interstitial fluid.
- Although the 1-sodium, 2-chloride, 1-potassium cotransporter moves equal amounts of cations and anions into the cell, there is a slight back leak of potassium ions into the lumen, creating a positive charge of about +8 millivolts in the tubular lumen.
- This positive charge forces cations such as Mg++ and Ca++ to diffuse from the tubular lumen through the paracellular space and into the interstitial fluid (Voltage drag).
- The thick ascending limb also has a sodium hydrogen counter-transport mechanism in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment.
- The thick segment of the ascending loop of Henle is virtually impermeable to water. Therefore, most of the water delivered to this segment remains in the tubule,
- The descending part of the thin segment of the loop of Henle is highly permeable to water and moderately permeable to most solutes but has few mitochondria and little or no active reabsorption.
- The thick ascending limb of the loop of Henle reabsorbs about 25 per cent of the filtered loads of sodium, chloride, and potassium, as well as large amounts of calcium, bicarbonate, and magnesium.

- This segment also secretes hydrogen ions into the tubular lumen. The tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule, a feature that is important in allowing the kidneys to dilute or concentrate the urine under different conditions.
- The thick segment of the ascending limb of the loop of Henle empties into the distal tubule.
- Distal Tubule
 - The very first portion of the distal tubule forms part of the juxtaglomerular complex that provides feedback control of GFR and blood flow in this same nephron.
 - Early Distal: The next part of the distal tubule is highly convoluted and has many of the same reabsorptive characteristics of the thick segment of the ascending limb of the loop of Henle. That is, it avidly reabsorbs most of the ions, including sodium, potassium, and chloride, but is virtually impermeable to water and urea. For this reason, it is referred to as the diluting segment because it also dilutes the tubular fluid. Approximately 5 percent of the filtered load of sodium chloride is reabsorbed in the early distal tubule.
 - The sodium-chloride co-transporter moves sodium chloride from the tubular lumen into the cell, and the sodium-potassium ATPase pump transports sodium out of the cell across the basolateral mem brane. Chloride diffuses out of the cell into the renal interstitial fluid through chloride channels in the basolateral membrane.
 - The **thiazide diuretics**, which are widely used to treat disorders such as hypertension and heart failure, inhibit the sodium chloride co-transporter.

Late Distal Tubule and Cortical Collecting Tubule

- The second half of the distal tubule and the subsequent cortical collecting tubule have similar functional characteristics.
- Anatomically, they are composed of two distinct cell types, the principal cells and the intercalated cells.
- **The principal** cells reabsorb sodium and water from the lumen and secrete potassium ions into the lumen.
- **The intercalated** cells reabsorb potassium ions and secrete hydrogen ions into the tubular lumen.

Principal Cells Reabsorb Sodium and Secrete Potassium

Sodium reabsorption and potassium secretion by the principal cells depend on the activity of a sodium potassium ATPase pump in each cell's basolateral membrane.

- This pump maintains a low sodium concentration inside the cell and, therefore, favors sodium diffusion into the cell through special Renal interstitial fluid Tubular lumen (-10mV) Tubular cells ATP Na+ Cl K+ Thiazide diuretics: Na+ Cl
- Mechanism of sodium chloride transport in the early distal tubule.
 Sodium and chloride are transported from the tubular lumen into the cell by a co-transporter that is inhibited by thiazide diuretics.
- Sodium is pumped out of the cell by sodium-potassium ATPase and chloride diffuses into the interstitial fluid via chloride channels.

- The early distal tubule has many of the same characteristics as the thick ascending loop of Henle and reabsorbs sodium, chloride, calcium, and magnesium but is virtually impermeable to water and urea.
- The reabsorption of water from this tubular segment is controlled by the concentration of antidiuretic hormones. channels.
- The secretion of potassium by these cells from the blood into the tubular lumen involves two steps:

(1) Potassium enters the cell because of the sodium-potassium ATPase pump, which maintains a high intracellular potassium concentration,

(2) once in the cell, potassium diffuses down its concentration gradient across the luminal membrane into the tubular fluid.

- The principal cells are the primary sites of action of the potassium-sparing diuretics, including spironolactone, eplerenone, amiloride, and triamterene.
- Aldosterone antagonists compete with aldosterone for receptor sites in the principal cells and therefore inhibit the stimulatory effects of aldosterone on sodium reabsorption and potassium secretion.
- Sodium channel blockers directly inhibit the entry of sodium into the sodium channels of the luminal membranes and therefore reduce the amount of sodium that can be transported across the basolateral membranes by the sodium-potassium ATPase pump. This, in turn, decreases transport of potassium into the cells and ultimately reduces potassium secretion into the tubular fluid. For this reason, the sodium channel blockers as well as the aldosterone antagonists decrease urinary excretion of potassium and act as **potassium-sparing diuretics**.
- Intercalated Cells
- Avidly Secrete Hydrogen and Reabsorb Bicarbonate and Potassium Ions.
- Hydrogen ion secretion by the intercalated cells is mediated by a hydrogen ATPase transport mechanism.
- Hydrogen is generated in this cell by the action of carbonic anhydrase on water and carbon dioxide to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions.
- The hydrogen ions are then secreted into the tubular lumen, and for each hydrogen ion secreted, a bicarbonate ion becomes available for reabsorption across the basolateral membrane.
- The intercalated cells can also reabsorb potassium ions.
- The functional characteristics of the late distal tubule and cortical collecting tubule

1. The tubular membranes of both segments are almost completely impermeable to urea, similar to the diluting segment of the early distal tubule; thus, almost all the urea that enters these segments passes on through and into the collecting duct to be excreted in the urine, although some reabsorption of urea occurs in the medullary collecting ducts.

2. Both the late distal tubule and the cortical collecting tubule segments reabsorb sodium ions, and the rate of reabsorption is controlled by hormones, especially aldosterone.

3. These segments secrete potassium ions from the peritubular capillary blood into the tubular lumen, a process that is also controlled by aldosterone and by other factors such as the concentration of potassium ions in the body fluids.

4. The intercalated cells of these nephron segments avidly secrete hydrogen ions by an active hydrogen-ATPase mechanism.

- This process is different from the secondary active secretion of hydrogen ions by the proximal tubule because it is capable of secreting hydrogen ions against a large concentration gradient, as much as 1000 to 1.
- This is in contrast to the relatively small gradient (4- to 10-fold) for hydrogen ions that can be achieved by secondary active secretion in the proximal tubule.
- Thus, the intercalated cells play a key role in acid-base regulation of the body fluids.
 5. The permeability of the late distal tubule and cortical collecting duct to water is controlled by the concentration of ADH, which is also called vasopressin. With high levels of ADH, these tubular segments are permeable to water, but in the absence of ADH, they are virtually impermeable to water.
- This special characteristic provides an important mechanism for controlling the degree of dilution or concentration of the urine.
- Medullary Collecting Duct

Although the medullary collecting ducts reabsorb less than 10 per cent of the filtered water and sodium, they are the final site for processing the urine and, therefore, play an extremely important role in determining the final urine output of water and solutes.

- The epithelial cells of the collecting ducts are nearly cuboidal in shape with smooth surfaces and relatively few mitochondria.
- Special characteristics of this tubular segment are as follows:

1. The permeability of the medullary collecting duct to water is controlled by the level of ADH. With high levels of ADH, water is avidly reabsorbed into the medullary interstitium, thereby reducing the urine volume and concentrating most of the solutes in the urine.

2. Unlike the cortical collecting tubule, the medullary collecting duct is permeable to urea. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping to raise the osmolality in this region of the kidneys and contributing to the kidneys' overall ability to form a concentrated urine.

3. The medullary collecting duct is capable of secreting hydrogen ions against a large concentration gradient, as also occurs in the cortical collecting tubule. Thus, the medullary collecting duct also plays a key role in regulating acid-base balance.

Summary of Concentrations of Different Solutes in the Different Tubular Segments

Whether a solute will become concentrated in the tubular fluid is determined by the relative degree of reabsorption of that solute versus the reabsorption of water.

- If a greater percentage of water is reabsorbed, the substance becomes more concentrated.
- If a greater percentage of the solute is reabsorbed, the substance becomes more diluted.
- ratio of tubular fluid/plasma concentration
- If plasma concentration of the substance is assumed to be constant, any change in the ratio of tubular fluid/plasma concentration rate reflects changes in tubular fluid concentration.
- As the filtrate moves along the tubular system, the concentration rises to progressively greater than 1.0 if more water is reabsorbed than solute,
- If there has been a net secretion of the solute into the tubular, the concentration ratio becomes progressively less than 1.0, this means that relatively more solute has been reabsorbed than water.

- Creatinine becomes highly concentrated in the urine as we move along. Like these substances they are not needed by the body, and the kidneys have become adapted to reabsorb them only slightly or not at all, or even to secrete them into the tubules, thereby excreting especially great quantities into the urine.
- In contrast, for less than 1 ratio, the substances such as glucose and amino acids, are all strongly reabsorbed; these are all substances that the body needs to conserve, and almost none of them are lost in the urine.
- A ratio value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same as the concentration of that substance in the plasma. Values below 1.0 indicate that the substance is reabsorbed more avidly than water, whereas values above 1.0 indicate that the substance is reabsorbed to a lesser extent than water or is secreted into the tubules.

• Tubular Fluid /Plasma Inulin Concentration Ratio Can Be Used to Measure Water Reabsorption by the Renal Tubules.

Inulin, a polysaccharide used to measure GFR, is not reabsorbed or secreted by the renal tubules.

- Changes in inulin concentration at different points along the renal tubule, therefore, reflect changes in the amount of water present in the tubular fluid.
- For example, the tubular fluid/plasma concentration ratio for inulin rises to about 3.0 at the end of the proximal tubules, indicating that inulin concentration in the tubular fluid is 3 times greater than in the plasma and in the glomerular filtrate.
- Since inulin is not secreted or reabsorbed from the tubules, a tubular fluid/plasma con centration ratio of 3.0 means that only one third of the water that was filtered remains in the renal tubule and that two thirds of the filtered water have been reabsorbed as the fluid passes through the proximal tubule.
- At the end of the collecting ducts, the tubular fluid/plasma inulin concentration ratio rises to about 125, indicating that only 1/125 of the filtered water remains in the tubule and that more than 99% has been reabsorbed.

• Regulation of Tubular Reabsorption

Because it is essential to maintain a precise balance between tubular reabsorption and glomerular filtration, there are multiple nervous, hormonal, and local control mechanisms that regulate tubular reabsorption, just as there are for control of glomerular filtration.

- An important feature of tubular reabsorption is that reabsorption of some solutes can be regulated independently of others, especially through hormonal control mechanisms.
- Glomerulotubular Balance—The Ability of the Tubules to Increase Reabsorption Rate in Response to Increased Tubular Load

One of the most basic mechanisms for controlling tubular reabsorption is the intrinsic ability of the tubules to increase their reabsorption rate in response to increased tubular load (increased tubular inflow).

- For example, if GFR is increased from 125 ml/ min to 150 ml/min, the absolute rate of proximal tubular reabsorption also increases from about 81 ml/ min (65 per cent of GFR) to about 97.5 ml/min (65 per cent of GFR).
- Thus, glomerulotubular balance refers to the fact that the total rate of reabsorption increases as the filtered load increases, even though the percentage of GFR reabsorbed in the proximal tubule remains relatively constant at about 65 per cent.
- Some degree of glomerulotubular balance also occurs in other tubular segments, especially the loop of Henle. The precise mechanisms responsible for this are not fully understood but may be due partly to changes in physical forces in the tubule and surrounding renal interstitium, as discussed later.
- It is clear that the mechanisms for glomerulotubular balance can occur independently of hormones and can be demonstrated in completely isolated kidneys or even in completely isolated proximal tubular segments.
- The importance of glomerulotubular balance is that it helps to prevent overloading of the distal tubular segments when GFR increases.
- Glomerulotubular balance acts as a second line of defense to buffer the effects of spontaneous changes in GFR on urine output. (The first line of defense, discussed earlier, includes the renal autoregulatory mechanisms, especially tubuloglomerular feedback, which help prevent changes in GFR.) Working together, the autoregulatory and glomerulotubular balance mechanisms prevent large changes in fluid flow in the distal tubules when the arterial pressure changes or when there are other disturbances that would otherwise disrupt the maintenance of sodium and volume homeostasis.
- **Peritubular Capillary and Renal Interstitial Fluid Physical Forces** Hydrostatic and colloid osmotic forces govern the rate of reabsorption across the peritubular capillaries, just as these physical forces control filtration in the glomerular capillaries.
- Changes in peritubular capillary reabsorption can in turn influence the hydrostatic and colloid osmotic pressures of the renal interstitium and, ultimately, reabsorption of water and solutes from the renal tubules.
- Normal Values for Physical Forces and Reabsorption Rate.

As the glomerular filtrate passes through the renal tubules, more than 99 per cent of the water and most of the solutes are normally reabsorbed.

- Fluid and electrolytes are reabsorbed from the tubules into the renal interstitium and from there into the peritubular capillaries.
- The normal rate of peritubular capillary reabsorption is about 124 ml/min.
- Reabsorption across the peritubular capillaries can be calculated as Reabsorption = Kf X Net reabsorptive force
- The net reabsorptive force represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose reabsorption across the peritubular capillaries.
- These forces include

(1) hydrostatic pressure inside the peritubular capillaries (peritubular hydro static pressure [Pc]), which opposes reabsorption.

(2) hydrostatic pressure in the renal interstitium (Pif) outside the capillaries, which favors reabsorption.

(3) colloid osmotic pressure of the peritubular capillary plasma proteins (pc), which favors reabsorption.

(4) colloid osmotic pressure of the proteins in the renal interstitium (pif), which opposes reabsorption.

- Because the normal peritubular capillary pressure averages about 13 mm Hg and renal interstitial fluid hydrostatic pressure averages 6 mm Hg, there is a positive hydrostatic pressure gradient from the peritubular capillary to the interstitial fluid of about 7 mm Hg, which opposes fluid reabsorption. This is more than counterbalanced by the colloid osmotic pressures that favor reabsorption.
- The plasma colloid osmotic pressure, which favors reabsorption, is about 32 mm Hg, and the colloid osmotic pressure of the interstitium, which opposes reabsorption, is 15 mm Hg, causing a net colloid osmotic force of about 17 mm Hg, favoring reabsorption.
- Therefore, subtracting the net hydrostatic forces that oppose reabsorption (7 mm Hg) from the net colloid osmotic forces that favor reabsorption (17 mm Hg) gives a net reabsorptive force of about 10 mm Hg.
- This is a high value, similar to that found in the glomerular capillaries, but in the opposite direction.
- The other factor that contributes to the high rate of fluid reabsorption in the peritubular capillaries is a large filtration coefficient (Kf) because of the high hydraulic conductivity and large surface area of the capillaries.
- Because the reabsorption rate is normally about 124 ml/min and net reabsorption pressure is 10 mm Hg, Kf normally is about 12.4 ml/min/mm Hg.
- Regulation of Peritubular Capillary Physical Forces.

The two determinants of peritubular capillary reabsorption that are directly influenced by renal hemodynamic changes are **the hydrostatic and colloid osmotic pressures** of the peritubular capillaries.

The peritubular capillary hydrostatic pressure is influenced by the arterial pressure and resistances of the afferent and efferent arterioles.

(1) Increases in arterial pressure tend to raise peritubular capillary hydrostatic pressure and decrease reabsorption rate. This effect is buffered to some extent by autoregulatory mechanisms that maintain relatively constant renal blood flow as well as relatively constant hydrostatic pressures in the renal blood vessels.

(2) Increase in resistance of either the afferent or the efferent arterioles reduce peritubular capillary hydrostatic pressure and tends to increase reabsorption rate. Although constriction of the efferent arterioles increases glomerular capillary hydrostatic pressure, it lowers peritubular capillary hydrostatic pressure.

The second major determinant of peritubular capillary reabsorption is the colloid osmotic **pressure** of the plasma in these capillaries.

Raising the colloid osmotic pressure increases peritubular capillary reabsorption. The colloid osmotic pressure of peritubular capillaries is determined by

(1) the systemic plasma colloid osmotic pressure; increasing the plasma protein con centration of systemic blood tends to raise peritubular capillary colloid osmotic pressure, thereby increasing reabsorption; and

(2) the filtration fraction; the higher the filtration fraction, the greater the fraction of plasma filtered through the glomerulus and, consequently, the more concentrated the protein becomes in the plasma that remains behind.

Thus, increasing the filtration fraction also tends to increase the peritubular capillary reabsorption rate. Because filtration fraction is defined as the ratio of GFR/renal plasma flow, increased filtration fraction can occur as a result of increased GFR or decreased renal plasma flow.

Some renal vasoconstrictors, such as angiotensin II,

increase peritubular capillary reabsorption by decreasing renal plasma flow and increasing filtration fraction, as discussed later.

Changes in the peritubular capillary Kf

Kf can also influence the reabsorption rate because Kf is a measure of the permeability and surface area of the capillaries. Increases in Kf raise reabsorption, whereas decreases in Kf lower peritubular capillary reabsorption. Kf remains relatively constant in most physiologic conditions. **Renal Interstitial Hydrostatic and Colloid Osmotic Pressures**.

Changes in peritubular capillary physical forces influence tubular reabsorption by changing the physical forces in the renal interstitium surrounding the tubules.

- For example, a decrease in the reabsorptive force across the peritubular capillary membranes, caused by either increased peritubular capillary hydrostatic pressure or decreased peritubular capillary colloid osmotic pressure, reduces the uptake of fluid and solutes from the interstitium into the peritubular capillaries.
- This in turn raises renal interstitial fluid hydrostatic pressure and decreases interstitial fluid colloid osmotic pressure because of dilution of the proteins in the renal interstitium.
- These changes then decrease the net reabsorption of fluid from the renal tubules into the interstitium, especially in the proximal tubules.
- The mechanisms by which changes in interstitial fluid hydrostatic and colloid osmotic pressures influence tubular reabsorption can be understood by examining the pathways through which solute and water are reabsorbed.
- Once the solutes enter the intercellular channels or renal interstitium by active transport or passive diffusion, water is drawn from the tubular lumen into the interstitium by osmosis.
- And once the water and solutes are in the interstitial spaces, they can either be swept up into the peritubular capillaries or diffuse back through the epithelial junctions into the tubular lumen.
- The tight junctions between the epithelial cells of the proximal tubule are actually leaky, so that considerable amounts of sodium can diffuse in both directions through these junctions.
- With the normal high rate of peritubular capillary reabsorption, the net movement of water and solutes is into the peritubular capillaries with little back leak into the lumen of the tubule. However, when peritubular capillary reabsorption is reduced, there is increased interstitial fluid hydrostatic pressure and a tendency for greater amounts of solute and water to back leak into the tubular lumen, thereby reducing the rate of net reabsorption.

- The opposite is true when there is increased peritubular capillary reabsorption above the normal level.
- An initial increase in reabsorption by the peritubular capillaries tends to reduce interstitial fluid hydrostatic pressure and raise interstitial fluid colloid osmotic pressure.
- Both of these forces favor movement of fluid and solutes out of the tubular lumen and into the interstitium; therefore, back leak of water and solutes into the tubular lumen is reduced, and net tubular reabsorption increases.
- Thus, through changes in the hydrostatic and colloid osmotic pressures of the renal interstitium, the uptake of water and solutes by the peritubular capillaries is closely matched to the net reabsorption of water and solutes from the tubular lumen into the interstitium.
- In general, forces that increase peritubular capillary reabsorption also increase reabsorption from the renal tubules. Conversely, hemodynamic changes that inhibit peritubular capillary reabsorption also inhibit tubular reabsorption of water and solutes.
- Effect of Arterial Pressure on Urine Output—The Pressure-Natriuresis and Pressure-Diuresis Mechanisms Even small increases in arterial pressure often cause marked increases in urinary excretion of sodium and water, phenomena that are referred to as pressure natriuresis and pressure diuresis. Because of the autoregulatory mechanisms increasing the arterial pressure between the limits of 75- and 160-mm Hg usually has only a small effect on renal blood flow and GFR.
 - 1. The slight increase in GFR that does occur contributes in part to the effect of increased arterial pressure on urine output. When GFR autoregulation is impaired, as often occurs in kidney disease, increases in arterial pressure cause much larger increases in GFR.
 - 2. A second effect of increased renal arterial pressure that raises urine output is that it decreases the percentage of the filtered load of sodium and water that is reabsorbed by the tubules.
- The mechanisms responsible for this effect include a slight increase in peritubular capillary hydrostatic pressure, especially in the vasa recta of the renal medulla, and a subsequent increase in the renal interstitial fluid hydrostatic pressure.
- An increase in the renal interstitial fluid hydrostatic pressure enhances back leak of sodium into the tubular lumen, thereby reducing the net reabsorption of sodium and water and further increasing the rate of urine output when renal arterial pressure rises.
 - 3. A third factor that contributes to the pressure natriuresis and pressure-diuresis mechanisms is reduced angiotensin II formation.
- Angiotensin II itself increases sodium reabsorption by the tubules; it also stimulates aldosterone secretion, which further increases sodium reabsorption.
- Decreased angiotensin II formation contributes to the decreased tubular sodium reabsorption that occurs when arterial pressure is increased.

- Hormonal Control of Tubular Reabsorption
- Precise regulation of body fluid volumes and solute concentrations requires the kidneys to excrete different solutes and water at variable rates, sometimes independently of one another.
- For example, when potassium intake is increased, the kidneys must excrete more potassium while maintaining normal excretion of sodium and other electrolytes.
- When sodium intake is changed, the kidneys must appropriately adjust urinary sodium excretion without major changes in excretion of other electrolytes.
- Several hormones in the body provide this specificity of tubular reabsorption for different electrolytes and water.
- Aldosterone Increases Sodium Reabsorption and Increases Potassium Secretion.
- Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex, is an important regulator of sodium reabsorption and potassium secretion by the renal tubules.
- The primary site of aldosterone action is on the principal cells of the cortical collecting tubule.
- The mechanism by which aldosterone increases sodium reabsorption while at the same time increasing potassium secretion is by stimulating the sodium-potassium ATPase pump on the basolateral side of the cortical collecting tubule membrane.
- Aldosterone also increases the sodium permeability of the luminal side of the membrane.
- Clinical Perspective
- In the absence of aldosterone, as occurs with adrenal destruction or malfunction (Addison's disease), there is marked loss of sodium from the body and accumulation of potassium.
- Excess aldosterone secretion, as occurs in patients with adrenal tumors (Conn's syndrome) is associated with sodium retention and potassium depletion.
- Although day-to-day regulation of sodium balance can be maintained as long as minimal levels of aldosterone are present, the inability to appropriately adjust aldosterone secretion greatly impairs the regulation of renal potassium excretion and potassium concentration of the body fluids.
- <u>Aldosterone is even more important as a regulator of potassium concentration than it is for</u> <u>sodium concentration</u>.
- Angiotensin II Increases Sodium and Water Reabsorption.
- Angiotensin II is perhaps the body's most powerful sodium-retaining hormone.
- Angiotensin II formation increases in circumstances associated with low blood pressure and/or low extracellular fluid volume, such as during hemorrhage or loss of salt and water from the body fluids.
- The increased formation of angiotensin II helps to return blood pressure and extracellular volume toward normal by increasing sodium and water reabsorption from the renal tubules through three main effects:

1. Angiotensin II stimulates aldosterone secretion, which in turn increases sodium reabsorption.

2. Angiotensin II constricts the efferent arterioles, which has two effects on peritubular capillary dynamics that raise sodium and water

First, efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules.

Second, efferent arteriolar constriction, by reducing renal blood flow, raises filtration fraction in the glomerulus and increases the concentration of proteins and the colloid osmotic pressure in the peritubular capillaries; this increases the reabsorptive force at the peritubular capillaries and raises tubular reabsorption of sodium and water.

- 4. Angiotensin II directly stimulates sodium reabsorption in the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules. By:
 - **First**: is to stimulate the sodium-potassium ATPase pump on the tubular epithelial cell basolateral membrane.
 - **Second**: is to stimulate sodium-hydrogen exchange in the luminal membrane, especially in the proximal tubule.
 - Thus, angiotensin II stimulates sodium transport across both the luminal and the basolateral surfaces of the epithelial cell membrane in the tubules.
- These multiple actions of angiotensin II cause marked sodium retention by the kidneys when angiotensin II levels are increased.

• ADH Increases Water Reabsorption.

The most important renal action of ADH is to increase the water permeability of the distal tubule, collecting tubule, and collecting duct epithelia.

- This effect helps the body to conserve water in circumstances such as dehydration.
- In the absence of ADH, the permeability of the distal tubules and collecting ducts to water is low, causing the kidneys to excrete large amounts of dilute urine.
- <u>The actions of ADH play a key role in controlling the degree of dilution or concentration of the urine</u>. ADH binds to specific V2 receptors in the late distal tubules, collecting tubules, and collecting ducts, increasing the formation of cyclic AMP and activating protein kinases. This, in turn, stimulates the movement of an intracellular protein, called aquaporin-2 (AQP2), to the luminal side of the cell membranes.
- The molecules of AQP-2 cluster together and fuse with the cell membrane by exocytosis to form water channels that permit rapid diffusion of water through the cells.
- There are other aquaporins, AQP-3 and AQP-4, in the basolateral side of the cell membrane that provide a path for water to rapidly exit the cells, although these are not believed to be regulated by ADH.
- Chronic increases in ADH levels also increase the formation of AQP-2 protein in the renal tubular cells by stimulating AQP-2 gene transcription.
- When the concentration of ADH decreases, the molecules of AQP-2 are shuttled back to the cell cytoplasm, thereby removing the water channels from the luminal membrane and reducing water permeability.
- Atrial Natriuretic Peptide Decreases Sodium and Water Reabsorption.

Specific cells of the cardiac atria, when distended because of plasma volume expansion, secrete a peptide called atrial natriuretic peptide.

• Increased levels of this peptide in turn inhibit the reabsorption of sodium and water by the renal tubules, especially in the collecting ducts.

• This decreased sodium and water reabsorption increases urinary excretion, which helps to return blood volume back toward normal.

• Parathyroid Hormone Increases Calcium Reabsorption.

Parathyroid hormone is one of the most important calcium-regulating hormones in the body.

- Its principal action in the kidneys is to increase tubular reabsorption of calcium, especially in the distal tubules and perhaps also in the loops of Henle.
- Parathyroid hormone also has other actions, including inhibition of phosphate reabsorption by the proximal tubule and stimulation of magnesium reabsorption by the loop of Henle,

• Sympathetic Nervous System Activation Increases Sodium Reabsorption

Activation of the sympathetic nervous system can decrease sodium and water excretion by constricting the renal arterioles, thereby reducing GFR.

Sympathetic activation also increases sodium reabsorption in the proximal tubule, the thick
ascending limb of the loop of Henle, and perhaps in more distal parts of the renal tubule. And
finally, sympathetic nervous system stimulation increases renin release and angiotensin II
formation, which adds to the overall effect to increase tubular reabsorption and decrease renal
excretion of sodium.

• Use of Clearance Methods to Quantify Kidney Function

The rates at which different substances are "cleared" from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances. **By definition**, the **renal clearance** of a substance is <u>the volume of plasma that is completely</u> <u>cleared of the substance by the kidneys per unit time.</u>

This concept is somewhat abstract because there is no single volume of plasma that is completely cleared of a substance.

 However, renal clearance provides a useful way of quantifying the excretory function of the kidneys and, can be used to quantify the rate at which blood flows through the kidneys as well as the basic functions of the kidneys: glomerular filtration, tubular reabsorption, and tubular secretion.

• The clearance principle:

If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter and if 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is "cleared" of the substance.

Thus, clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit time.

- Stated mathematically, Cs X Ps = Us X V, where Cs is the clearance rate of a substance s, Ps is the plasma concentration of the substance, us is the urine concentration of that substance, and V is the urine flow rate.
- Rearranging this equation, clearance can be expressed as Thus, renal clearance of a substance is calculated from the urinary excretion rate (Us ¥ V) of that substance divided by its plasma concentration.

• Inulin Clearance Can Be Used to Estimate GFR

If a substance is freely filtered (filtered as freely as water) and is not reabsorbed or secreted by the renal tubules, then the rate at which that substance is excreted in the urine (Us X V) is equal to the filtration rate of the substance by the kidneys (GFR X Ps). Thus, GFR X Ps = Us X V.

- The GFR, therefore, can be calculated as the clearance of the substance as follows: A substance that fits these criteria is inulin, a polysaccharide molecule, which is not produced in the body, is found in the roots of certain plants and must be administered intravenously to a patient to measure GFR.
- Example: the plasma concentration is 1 mg/ml, urine concentration is 125 mg/ml, and urine flow rate is 1 ml/ min. Therefore, 125 mg/min of inulin passes into the urine. Then, inulin clearance is calculated as the urine excretion rate of inulin divided by the plasma concentration, which yields a value of 125 ml/min. Thus, 125 milliliters of plasma flowing through the kidneys must be filtered to deliver the inulin that appears in the urine.
- Inulin is not the only substance that can be used for determining GFR. Other substances that have been used clinically to estimate GFR include <u>radioactive iothalamate and creatinine</u>.
- Creatinine Clearance and Plasma Creatinine Concentration Can Be Used to Estimate GFR Creatinine is a by-product of muscle metabolism and is cleared from the body fluids almost entirely by glomerular filtration.
- Therefore, the clearance of creatinine can also be used to assess GFR.
- Because measurement of creatinine clearance does not require intravenous infusion into the patient, this method is much more widely used than inulin clearance for estimating GFR clinically.
- However, creatinine clearance is not a perfect marker of GFR because a small amount of it is secreted by the tubules, so that the amount of creatinine excreted slightly exceeds the amount filtered.
- There is normally a slight error in measuring plasma creatinine that leads to an overestimate of the plasma creatinine concentration (because part of creatinine is bound to plasma protein but still measured although is not filtered), and these two errors tend to cancel each other.
- Therefore, creatinine clearance provides a reasonable estimate of GFR.
- In some cases, it may not be practical to collect urine in a patient for measuring creatinine clearance (CCr). An approximation of changes in GFR, however, can be obtained by simply measuring plasma creatinine concentration (PCr), which is inversely proportional to GFR: If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing accumulation of creatinine in the body fluids and raising plasma concentration.

- Plasma concentration of creatinine will continue to rise until the filtered load of creatinine (PCr X GFR) and creatinine excretion (UCr X V) return to normal and a balance between creatinine production and creatinine excretion is reestablished. This will occur when plasma creatinine increases to approximately twice normal,
- If GFR falls to one-fourth normal, plasma creatinine would increase to about 4 times normal, and a decrease of GFR to one-eighth normal would raise plasma creatinine to 8 times normal.
- Thus, under steadystate conditions, the creatinine excretion rate equals the rate of creatinine production, despite reductions in GFR.
- However, this normal rate of creatinine excretion occurs at the expense of elevated plasma creatinine concentration,
- PAH Clearance Can Be Used to Estimate Renal Plasma Flow

Theoretically, if a substance is completely cleared from the plasma, the clearance rate of that substance is equal to the total renal plasma flow.

- In other words, the amount of the substance delivered to the kidneys in the blood (renal plasma flow X Ps) would be equal to the amount excreted in the urine (Us X V).
- Thus, renal plasma flow (RPF) could be calculated as = UsX V/ Ps
- Because the GFR is only about 20 per cent of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion as well as glomerular filtration.
- There is no known substance that is completely cleared by the kidneys.
- However, PAH, is about 90 per cent cleared from the plasma. Thus, the clearance of PAH can be used as an approximation of renal plasma flow.
- To be more accurate, one can correct for the percentage of PAH that is still in the blood when it leaves the kidneys.
- The percentage of PAH removed from the blood is known as **the extraction ratio of PAH** and averages about **90 per cent** in normal kidneys.
- In diseased kidneys, this extraction ratio may be reduced because of the inability of damaged tubules to secrete PAH into the tubular fluid.
- The calculation of RPF can be demonstrated by the following example: Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min. PAH clearance can be calculated from the rate of urinary PAH excretion (5.85 mg/ml X 1 ml/min) divided by the plasma PAH concentration (0.01 mg/ml).
- Thus, clearance of PAH calculates to be 585 ml/min. If the extraction ratio for PAH is 90 per cent, the actual renal plasma flow can be calculated by dividing 585 ml/min by 0.9, giving a value of 650 ml/min.
- Thus, total renal plasma flow can be calculated as Total renal plasma flow = Clearance of PAH/Extraction ratio of PAH
- The extraction ratio (EPAH) is calculated as the difference between the renal arterial PAH (PPAH) and renal venous PAH (VPAH) concentrations, divided by the renal arterial PAH concentration:

- You can calculate the total blood flow through the kidneys from the total renal plasma flow and hematocrit (the percentage of red blood cells in the blood).
- If the hematocrit is 0.45 and the total renal plasma flow is 650 ml/min, the total blood flow through both kidneys is 650/(1 0.45), or 1182 ml/min.
- Filtration Fraction Is Calculated from GFR Divided by Renal Plasma Flow
 To calculate the filtration fraction, which is the fraction of plasma that filters through the
 glomerular membrane, you must first know the renal plasma flow (PAH clearance) and the GFR
 (inulin clearance). If renal plasma flow is 650 ml/min and GFR is 125 ml/min, the filtration
 fraction (FF) is calculated as FF = GFR/RPF = 125/650 = 0.19
- Calculation of Tubular Reabsorption or Secretion from Renal Clearances If the rates of glomerular filtration and renal excretion of a substance are known, you can calculate whether there is a net reabsorption or a net secretion of that sub stance by the renal tubules.
- For example, if the rate of excretion of the substance (Us X V) is less than the filtered load of the substance (GFR X Ps), then some of the substance must have been reabsorbed from the renal tubules.
- Conversely, if the excretion rate of the substance is greater than its filtered load, then the rate at which it appears in the urine represents the sum of the rate of glomerular filtration plus tubular secretion.
- The following example demonstrates the calculation of tubular reabsorption: Assume the following laboratory values for a patient were obtained: Plasma creatinine concentration (mg/100 ml) Glomerular filtration rate (ml/min) Urine flow rate = 1 ml/min Urine concentration of sodium (UNa) = 70 mEq/L = 70 mEq/ml Plasma sodium concentration = 140 mEq/L = 140 mEq/ml GFR (inulin clearance) = 100 ml/min In this example, the filtered sodium load is GFR X PNa, or 100 ml/min X 140 mEq/ml = 14,000 mEq/min. Urinary sodium excretion (UNa X urine flow rate) is 70 mEq/min. Therefore, tubular reabsorption of sodium is the difference between the filtered load and urinary excretion, or 14,000 mEq/min - 70 mEq/min = 13,930 mEq/min.

• Comparisons of Inulin Clearance with Clearances of Different Solutes.

The following generalizations can be made by comparing the clearance of a substance with the clearance of inulin, a measure of GFR:

(1) if the clearance rate of the substance equals that of inulin, the substance is only filtered and not reabsorbed or secreted;

(2) if the clearance rate of a substance is less than inulin clearance, the substance must have been reabsorbed by the nephron tubules;

(3) if the clearance rate of a sub stance is greater than that of inulin, the substance must be secreted by the nephron tubules.

• The approximate clearance rates for some of the substances normally handled by the kidneys: Substance Clearance Rate (ml/min): Glucose 0, Sodium 0.9, Chloride 1.3, Potassium 12.0, Phosphate 25.0, Inulin 125.0, Creatinine 140.

Reference:

Guyton and Hall Text Book of Medical Physiology, first Jordanian edition