PHYSIOLOGY

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LECTURE 10, PART (2): RENAL PHYSIOLOGY

Objectives

1. Discuss **glomerular filtration rate and regulation of GFR.**
2. Describe **tubular reabsorption**.
3. Explore **homeostatic regulation of tubular reabsorption and tubular secretion.**
4. Discuss **production of dilute and concentrated urine, evaluation of kidney function, and renal plasma clearance.**

(Pages 993- 1014 of the reference)

NET FILTRATION PRESSURE

Figure 26.9 The pressures that drive glomerular filtration

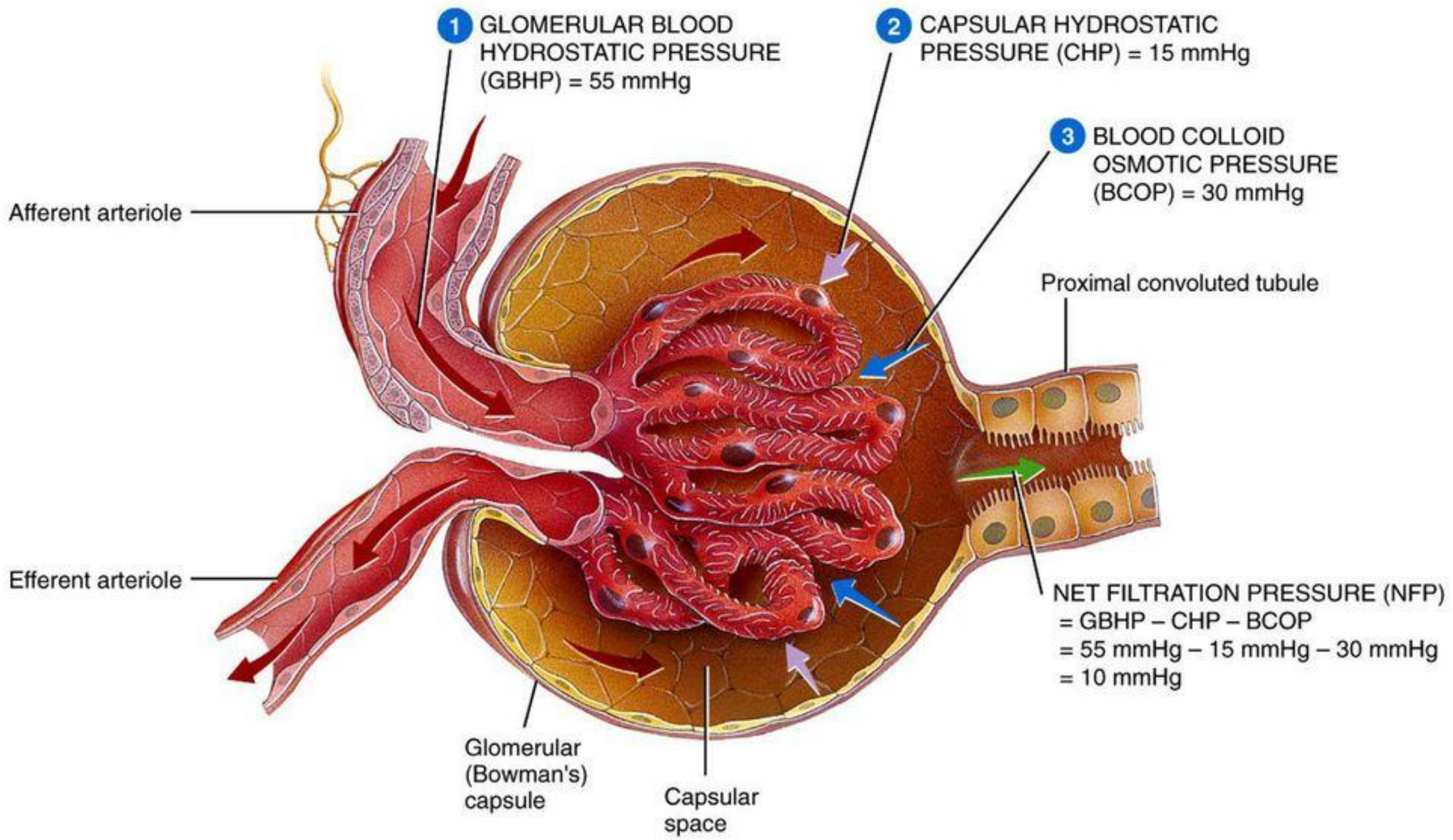


Figure 26.09 Tortora - PAP 12/e

Glomerular filtration depends on three main pressures. One pressure promotes filtration, and two pressures oppose filtration.

Glomerular blood hydrostatic pressure promotes filtration, whereas capsular hydrostatic pressure and blood colloid osmotic pressure oppose filtration.

NET FILTRATION PRESSURE

- **Glomerular blood hydrostatic pressure (GBHP)** is the blood pressure in glomerular capillaries. Generally, GBHP is about 55 mmHg (millimetre of mercury). It promotes filtration by forcing water and solutes in blood plasma through the filtration membrane.

- **Capsular hydrostatic pressure (CHP)** is the hydrostatic pressure exerted against the filtration membrane by fluid already in the capsular space and renal tubule. CHP opposes filtration and represents a "back pressure" of about 15 mmHg.

- **Blood colloid osmotic pressure (BCOP)**, which is due to the presence of proteins such as albumin, globulins, and fibrinogen in blood plasma, also opposes filtration. The average BCOP in glomerular capillaries is 30 mmHg.

NET FILTRATION PRESSURE

Net filtration pressure (NFP), the total pressure that promotes filtration, is determined as follows:

$$\text{Net filtration pressure (NFP)} = \text{GBHP} - \text{CHP} - \text{BCOP}$$

By substituting the values just given, normal NFP may be calculated:

$$\begin{aligned} \text{NFP} &= 55 \text{ mmHg} - 15 \text{ mmHg} - 30 \text{ mmHg} \\ &= 10 \text{ mmHg} \end{aligned}$$

Thus, a pressure of only 10 mmHg causes a normal amount of blood plasma (minus plasma proteins) to filter from the glomerulus into the capsular space.

GLOMERULAR FILTRATION RATE

- <u>The amount of filtrate formed in all renal corpuscles of both kidneys each minute</u> is the **glomerular filtration rate (GFR).**

سرعة الكمية التي تدخل من الكبسولة على tubules بالدقيقة

- In adults, the **GFR averages** 125 mL/min in males and 105 mL/min in females. كلما كان blood volume أكبر كلما كان filteration أعلى

وبالتالي بزيد filteration rate ولو صار vasconstruction في afferent arterioles حيقل blood flow ويقل filteration rate

- **Homeostasis of body fluids** requires that the <u>kidneys maintain a relatively constant GFR</u>.

GLOMERULAR FILTRATION RATE

- **<u>If the GFR is too high</u>**, needed substances may pass so quickly through the renal tubules that some are not reabsorbed and are lost in the urine.

- **<u>If the GFR is too low</u>**, nearly all the filtrate may be reabsorbed and certain waste products may not be adequately excreted.

- **GFR is directly related to the pressures that determine net filtration pressure**; any change in net filtration pressure will affect GFR.

اي تغير في ضغط الدم رح يأثر على GFR

أذا GFR عالي ← حيدفق السائل الفلتر في tubules بسرعة ← سوف يقل reabsorbtion ← حيصير secreation
لأشياء
الجسم
يحتاجها

إذا GFR قليل ← حينتقل السائل الفلتر في tubule ببطئ ← حيزيد reabsorbtion ← حيصير reabsorbtion
لأشياء الجسم ما بحتاجها
وممكن تكون ضارة على الجسم

GLOMERULAR FILTRATION RATE

- **The mechanisms that regulate glomerular filtration rate operate in two main ways**:
- (1) **by adjusting blood flow into and out of the glomerulus**. GFR increases when blood flow into the glomerular capillaries increases.
- (2) **by altering the glomerular capillary surface area available for filtration**. Coordinated control of the diameter of both afferent and efferent arterioles regulates glomerular blood flow. Constriction of the afferent arteriole decreases blood flow into the glomerulus; dilation of the afferent arteriole increases it.
- **Three mechanisms control GFR: <u>renal autoregulation, neural regulation, and hormonal regulation.</u>**

إلها علاقة بال
sympathetic

- كلما كانت كمية الدم (blood Volume) الواصل من afferent arterioles على الكلية أعلى كلما كانت GFR أعلى والعكس صحيح

cardiac output

- cardiac output يتناسب طرديا مع GFR لأنو الجسم لما يكون CO فيه عالي معناتو BP عالي blood flow
وبالتالي حو ليدي بحاجة لزيادة ضغط الدم من خلال زيادة reabsorption ، فزيادة CO بتزيد على afferent arterioles و بالتالي بتزيد GFR و تقل reabsorption لأن الجسم مش بحاجة انو water يرجع على systemic circulation و يزيد الضغط لأنو الضغط اصلا عالي

- لكن لو صار bleeding رح يقل BP وبالتالي رح يصير vasoconstriction لـ afferent arterioles و يقل GFR فحيزيد reabsorption لـ Na , water فيزداد blood Volume و يزداد BP و برأنو رح يرجع RAAS

RENAL AUTOREGULATION OF GFR

- The kidneys themselves help **maintain a constant renal blood flow and GFR despite normal**, **everyday changes in blood pressure**, like those that occur during exercise. This capability is called **renal autoregulation**.

- It consists of two mechanisms—the **myogenic mechanism** and **tubuloglomerular feedback. Working together, they can maintain nearly constant GFR over a wide range of systemic blood pressures.**

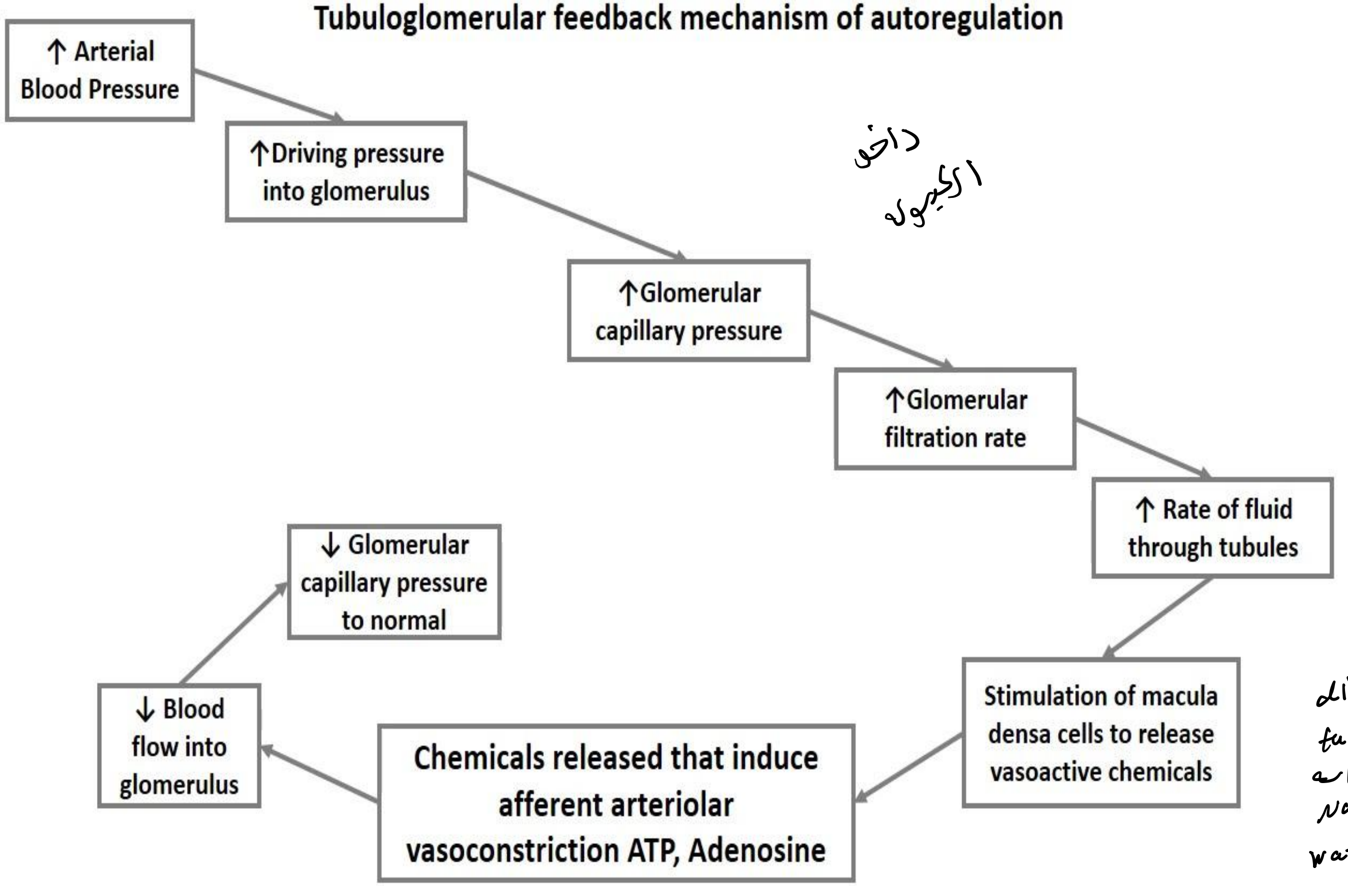
RENAL AUTOREGULATION OF GFR

- The **<u>myogenic mechanism</u>** occurs when stretching triggers contraction of smooth muscle cells in the walls of afferent arterioles. As blood pressure rises, GFR also rises because renal blood flow increases. However, the elevated blood pressure stretches the walls of the afferent arterioles, which narrows the arteriole's lumen. As a result, renal blood flow decreases, thus reducing GFR to its previous level.

RENAL AUTOREGULATION OF GFR

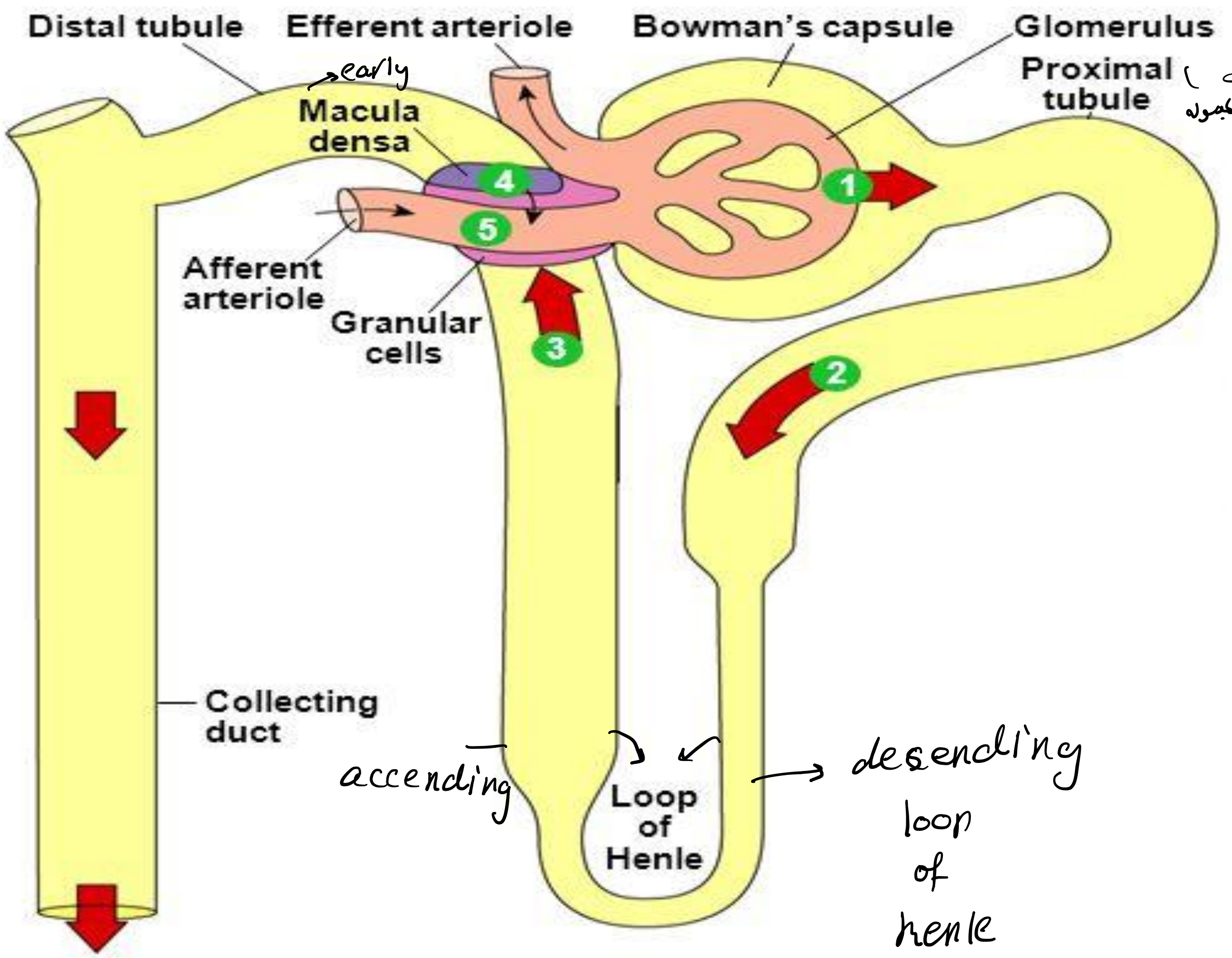
- The **second contributor to renal autoregulation**, **tubuloglomerular feedback**, is so named because part of the renal tubules—the macula densa (is an area of closely packed specialized cells lining the wall of the distal tubule, at the point where the thick ascending limb of the Loop of Henle meets the distal convoluted tubule.)—provides feedback to the glomerulus.

Tubuloglomerular feedback mechanism of autoregulation



distal tubuls
حساس
Na لل
water و

Tubuloglomerular Feedback



1. GFR increases.
2. Flow through tubule increases.
3. Flow past macula densa increases.
4. Paracrine diffuses from macula densa to afferent arteriole.
5. Afferent arteriole constricts.

↓

Resistance in afferent arteriole increases.

↓

Hydrostatic pressure in glomerulus decreases.

↓

GFR decreases.

NEURAL REGULATION OF GFR

- Like most blood vessels of the body, those of the kidneys are supplied by sympathetic ANS fibers that release norepinephrine.

Sympathetic agent. يوازي عدم إعطاء اي جرعة من

- **At rest**, sympathetic stimulation is moderately low, the afferent and efferent arterioles are dilated, and renal autoregulation of GFR prevails.

dominenent (dominanet)

Sympathetic agent يوازي جرعة متوسطة من

- **With moderate sympathetic stimulation**, both afferent and efferent arterioles constrict to the same degree. Blood flow into and out of the glomerulus is restricted to the same extent, which decreases GFR only slightly.

NEURAL REGULATION OF GFR

sympathetic agent يوازي جرعة عالية من

جداً عالي

- **With greater sympathetic stimulation**, however, as occurs during exercise or hemorrhage, vasoconstriction of the afferent arterioles predominates. As a result, blood flow into glomerular capillaries is greatly decreased, and GFR drops.

GFR حيقلل اكثر اشي

sympathetic activation = parasympathetic inactivation

- **This lowering of renal blood flow has two consequences:** (1) It reduces urine output, which helps conserve blood volume. (2) It permits greater blood flow to other body tissues.

HORMONAL REGULATION OF GFR

Two hormones contribute to regulation of GFR:

1. Angiotensin II (very potent vasoconstrictor) reduces GFR.

2. Atrial natriuretic peptide (ANP) increases GFR because ANP increases the capillary surface area available for filtration. بتشجيع إدرار البول فيقلل الضغط

TABLE 26.2

Regulation of Glomerular Filtration Rate (GFR)

TYPE OF REGULATION	MAJOR STIMULUS	MECHANISM AND SITE OF ACTION	EFFECT ON GFR
Renal autoregulation			
Myogenic mechanism	Increased stretching of smooth muscle fibers in afferent arteriole walls due to increased blood pressure.	Stretched smooth muscle fibers contract, thereby narrowing lumen of afferent arterioles.	Decrease.
Tubuloglomerular feedback	Rapid delivery of Na^+ and Cl^- to the macula densa due to high systemic blood pressure.	Vasodilator هو NO Decreased release of nitric oxide (NO) by juxtaglomerular apparatus causes constriction of afferent arterioles.	Decrease.
Neural regulation	Increase in activity level of renal sympathetic nerves releases norepinephrine.	Constriction of afferent arterioles through activation of α_1 receptors and increased release of renin.	Decrease.
Hormone regulation			
Angiotensin II	Decreased blood volume or blood pressure stimulates production of angiotensin II.	Constriction of afferent and efferent arterioles.	Decrease.
Atrial natriuretic peptide (ANP)	Stretching of atria of heart stimulates secretion of ANP.	Relaxation of mesangial cells in glomerulus increases capillary surface area available for filtration.	Increase.

شرح إضافي غير مطلوب
للفهم فقط

mesangial cells

خلايا الميسانجيال موجودة في الكبيبة وتحيط بالأوعية الدموية الكبيبية .

- عندما تنقبض خلايا الميسانجيال ، فإنها تقلل من المساحة المتاحة بين الشعيرات الدموية ، مما يؤثر على المساحة السطحية للترشيح . هذا يمكن أن يقلل من معدل الترشيح الكبيبي (GFR) .
- عندما ترتخي خلايا الميسانجيال ، فإنها تزيد من المساحة السطحية المتاحة للترشيح ، مما يمكن أن يزيد من GFR

TUBULAR REABSORPTION AND TUBULAR SECRETION

- **Reabsorption:**
  - The return of most of the filtered water and many of the filtered solutes (as sodium, potassium, chloride, bicarbonate and phosphate ions) to the bloodstream.

- **Tubular secretion**:
  - the transfer of materials (as hydrogen, potassium ions and ammonium ions, creatinine, and certain drugs such as penicillin) from the blood and tubule cells into glomerular filtrate. Tubular secretion has two important outcomes:
  - (1) The secretion of hydrogen ions helps control blood pH.
  - (2) The secretion of other substances helps eliminate them from the body in urine

Substances Filtered, Reabsorbed, and Excreted in Urine per Day

TABLE 21.1

Substances Filtered, Reabsorbed, and Excreted in Urine per Day

SUBSTANCE	FILTERED* (ENTERS RENAL TUBULE)	REABSORBED (RETURNED TO BLOOD)	SECRETED IN URINE
Water	180 liters	178–179 liters	1–2 liters
Chloride ions (Cl^-)	640 g	633.7 g	6.3 g
Sodium ions (Na^+)	579 g	575 g	4 g
Bicarbonate ions (HCO_3^-)	275 g	274.97 g	0.03 g
Glucose	162 g	162 g	0
Urea	54 g	24 g	30 g†
Potassium ions (K^+)	29.6 g	29.6 g	2.0 g‡
Uric acid	8.5 g	7.7 g	0.8 g
Creatinine	1.6 g	0	1.6 g

(المفروض ما يطلع من Kidney
وإذا كان في urine حيكون
معاه سكري)

المفروض ما يصير إله reabsorbtion
لأنه بطلع من wastes skeletal mucsle

*Assuming glomerular filtration is 180 liters per day.
†In addition to being filtered and reabsorbed, urea is secreted.
‡After virtually all filtered K^+ is reabsorbed in the convoluted tubules and loop of Henle, a variable amount of K^+ is secreted in the collecting duct.

REABSORPTION ROUTES

Reabsorption Routes

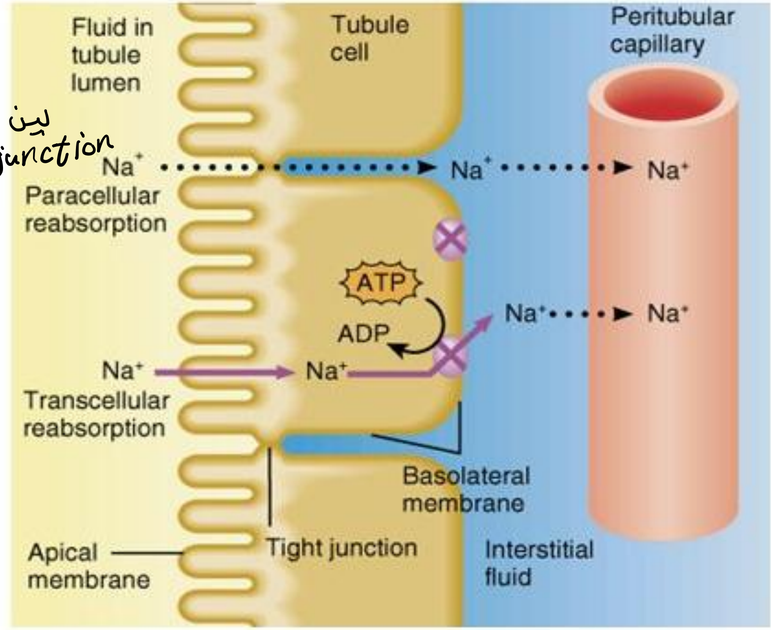
بين الخلايا

- Paracellular reabsorption
  - 50% of reabsorbed material moves between cells by diffusion in some parts of tubule

tight junction بين

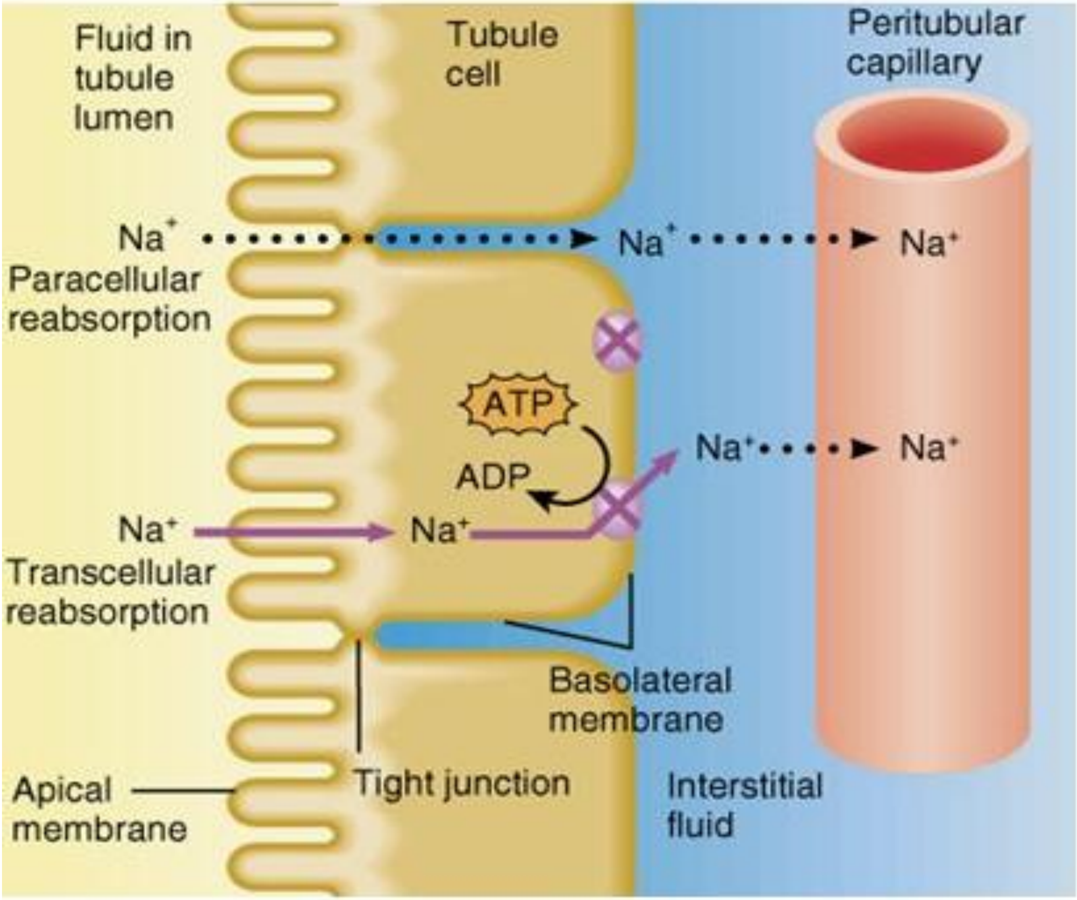
عبور داخل الخلية

- Transcellular reabsorption
  - material moves through both the apical and basal membranes of the tubule cell by active transport



✓ **In the renal system, peritubular capillaries** are tiny blood vessels, supplied by the efferent arteriole, that travel alongside nephrons allowing reabsorption and secretion between blood and the inner lumen of the nephron.

REABSORPTION ROUTES



- ✓ The apical membrane contacts the tubular fluid, and the basolateral membrane contacts interstitial fluid at the base and sides of the cell.

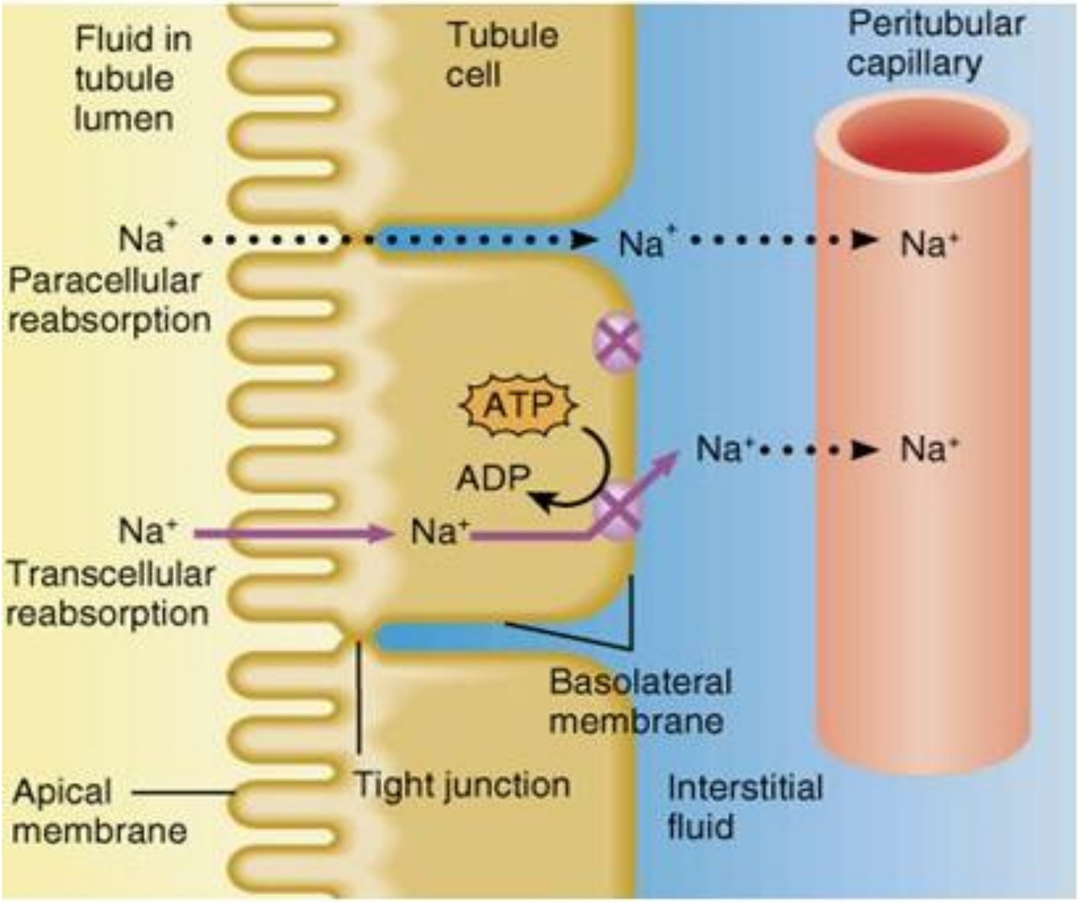
جوا tubule يكون في خلايا

- ✓ Even though the epithelial cells are connected by tight junctions, the tight junctions between cells in the proximal convoluted tubules are "leaky" and permit some reabsorbed substances to pass between cells into peritubular capillaries.

بمنع tight junction يصير mixing
للأشياء الي بتعبر من apical لل basolateral

مرات في اشياء مجبورة لل secretion و reabsorbtion في الجهة الثانية

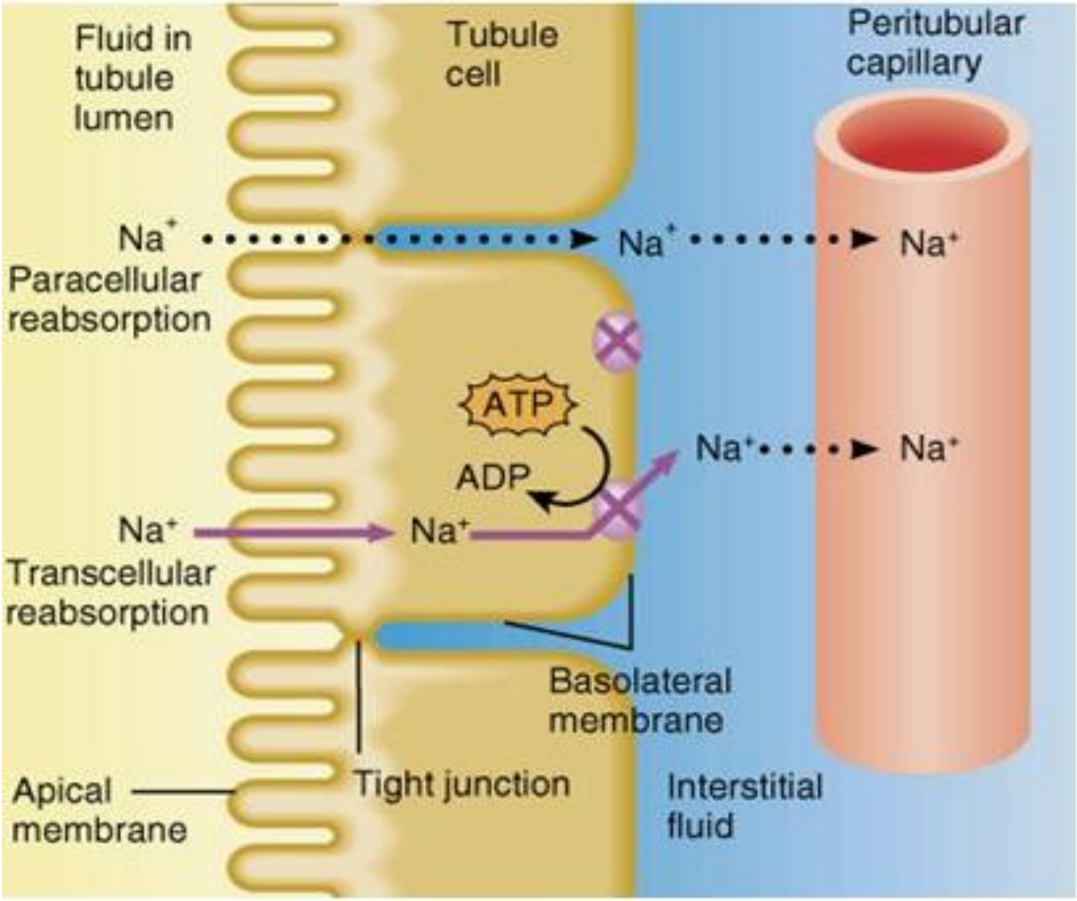
TRANSPORT MECHANISMS



- ✓ **In transcellular reabsorption, a substance passes from the fluid in the tubular lumen through the apical membrane of a tubule cell, across the cytosol, and out into interstitial fluid through the basolateral membrane.**

- ✓ **When renal cells transport solutes out of or into tubular fluid, they move specific substances in one direction only. Not surprisingly, different types of transport proteins are present in the apical and basolateral membranes. The tight junctions form a barrier that prevents mixing of proteins in the apical and basolateral membrane compartments.**

TRANSPORT MECHANISMS



- ✓ **Each type of transporter has an upper limit on how fast it can work**, just as an escalator has a limit on how many people it can carry from one level to another in a given period. **This limit, called the transport maximum (Tm), is measured in mg/min.** الحد الأعلى الي بتقدر تشيل فيه مواد

- ✓ Cells lining the renal tubules, like other cells throughout the body, have a low concentration of sodium ions in their cytosol due to the activity of sodium–potassium pumps. These pumps are located in the basolateral membranes and eject sodium ions from the renal tubule cells. The absence of sodium–potassium pumps in the apical membrane ensures that reabsorption of sodium ions is a one-way process.

TUBULAR REABSORPTION

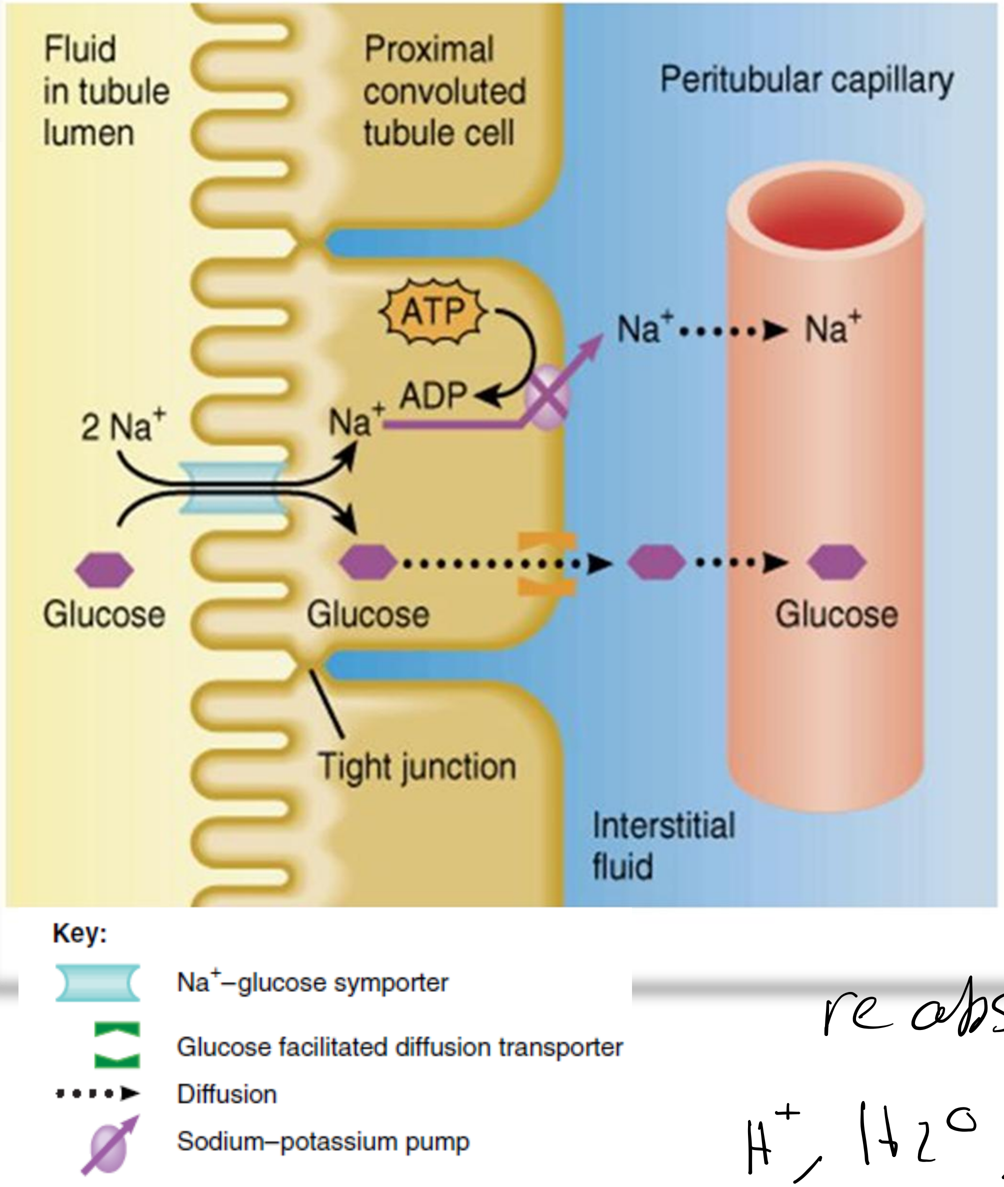
- Solute reabsorption drives water reabsorption because all water reabsorption occurs via osmosis. About 90% of the reabsorption of water filtered by the kidneys occurs along with the reabsorption of solutes such as sodium and chloride ions, and glucose.
- Water reabsorbed with solutes in tubular fluid is termed obligatory water reabsorption because the water is "obliged" to follow the solutes when they are reabsorbed. This type of water reabsorption occurs in the proximal convoluted tubule and the descending limb of the nephron loop.
- Reabsorption of the final 10% of the water, a total of 10–20 liters per day, is termed facultative water reabsorption. Facultative water reabsorption is regulated by antidiuretic hormone and occurs mainly in the collecting ducts.

REABSORPTION AND SECRETION IN THE PROXIMAL CONVOLUTED TUBULE

- ✓ **The largest amount of solute and water reabsorption from filtered fluid occurs in the proximal convoluted tubules.**

معظم reabsorbtion للماء و Na
يحدث في proximal tubule

Reabsorption of Glucose in PCT

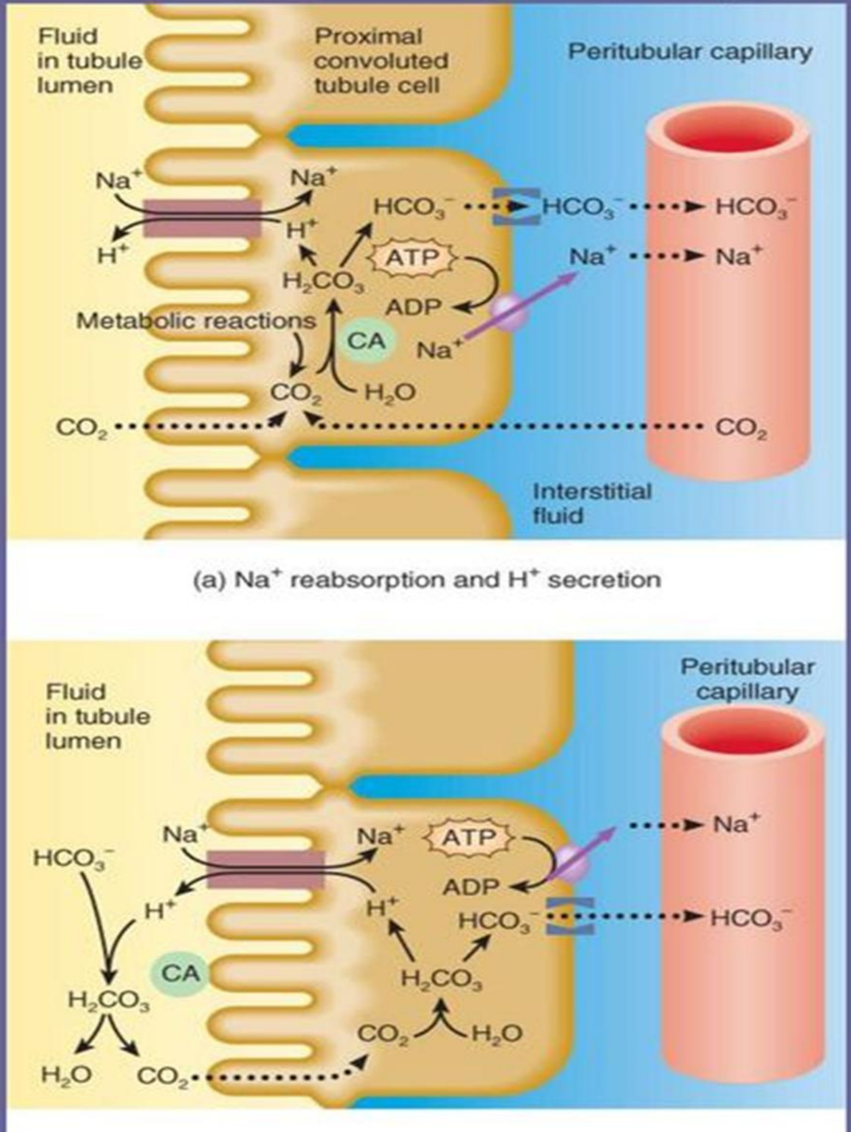


- Intracellular sodium levels are kept low due to Na^+/K^+ ATPase pump on basolateral membrane
- Low intracellular Na+ creates concentration gradient
  - high in filtrate – low in cell
- Na^+ **symporters** on apical membrane use energy from gradient to bring in glucose
  - **Secondary active transport**
- 2 Na^+ and 1 glucose attach to symporter and enter cell together
- Glucose then diffuses out of cell and into peritubular capillaries

الإشي إلى بصير إلو reabsorbtion

في proximal tubule هو جلوكوز و Na^+, HCO_3^-, Cl^-, H_2O, H^+

Reabsorption of Bicarbonate, Na+ & H+ Ions

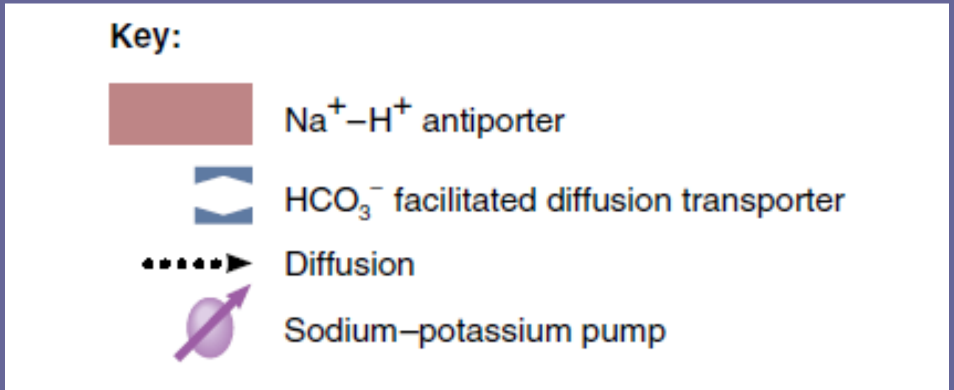


(a) Na^+ reabsorption and H^+ secretion

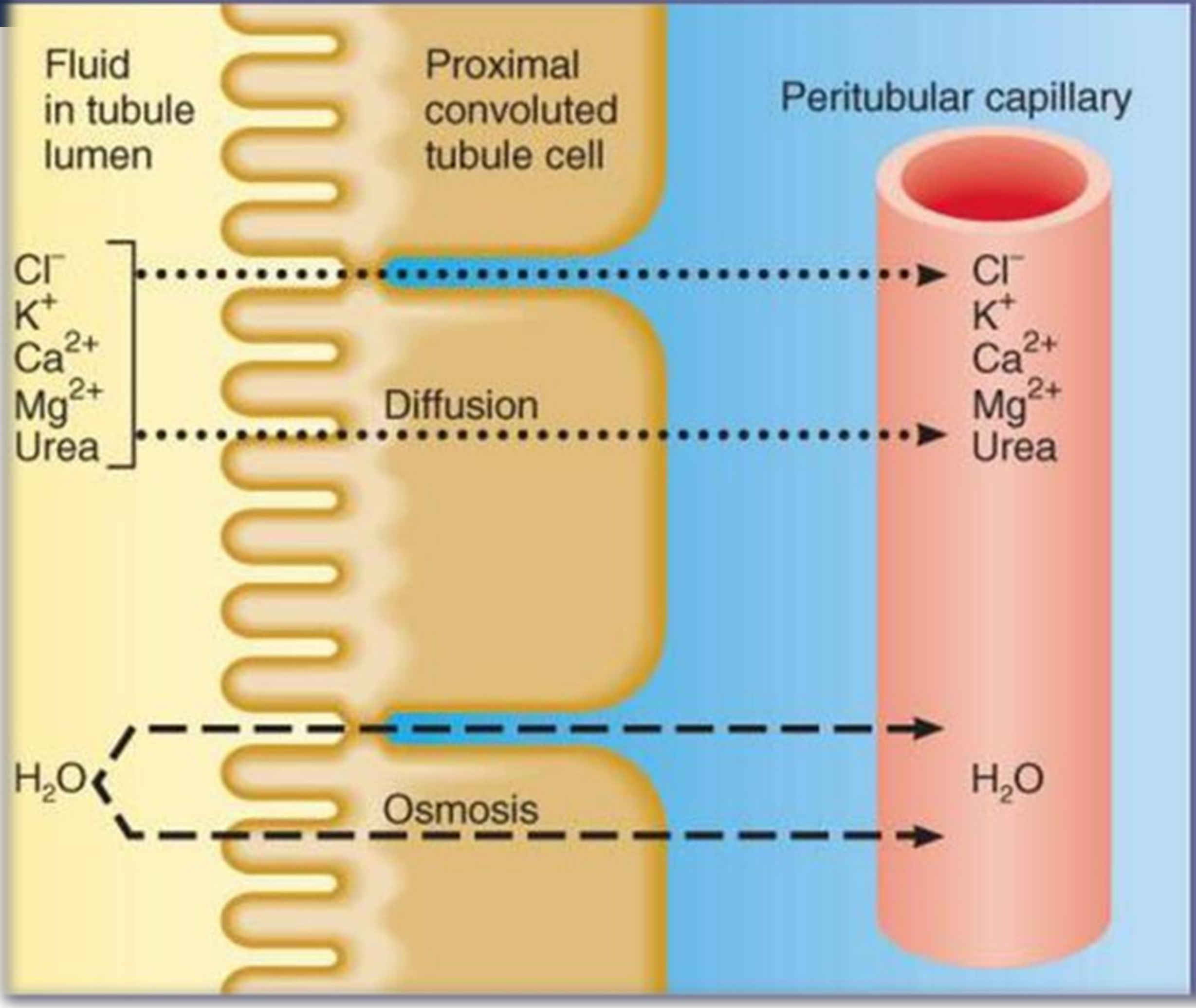
(b) HCO_3^- reabsorption

- Na+ antiporters reabsorb Na+ and secrete H+
  - PCT cells produce the H+ & release bicarbonate ion to the peritubular capillaries

    proximal convluated tubules
  - important buffering system
- For every H+ secreted into the tubular fluid, one filtered bicarbonate eventually returns to the blood



Passive Reabsorption in the 2nd Half of PCT

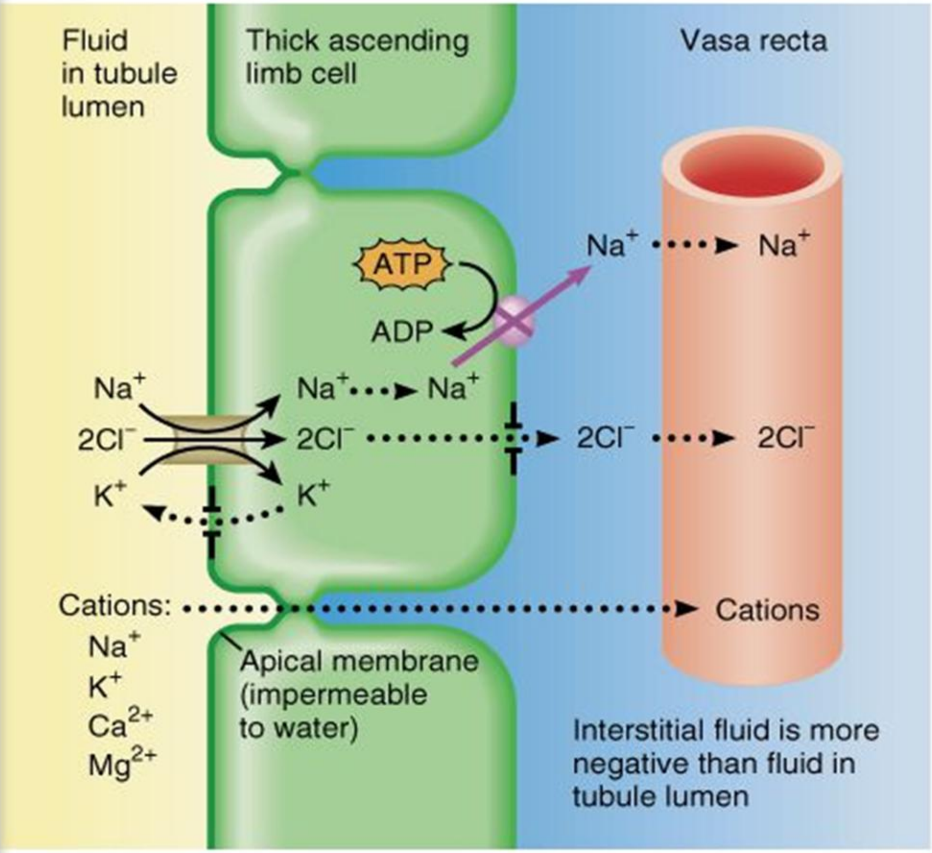


- Electrochemical gradients produced by symporters & antiporters causes passive reabsorption of other solutes
- Cl-, K+, Ca+2, Mg+2 and urea passively diffuse into the peritubular capillaries
- Promotes osmosis in PCT (especially permeable due to aquaporin-1 channels

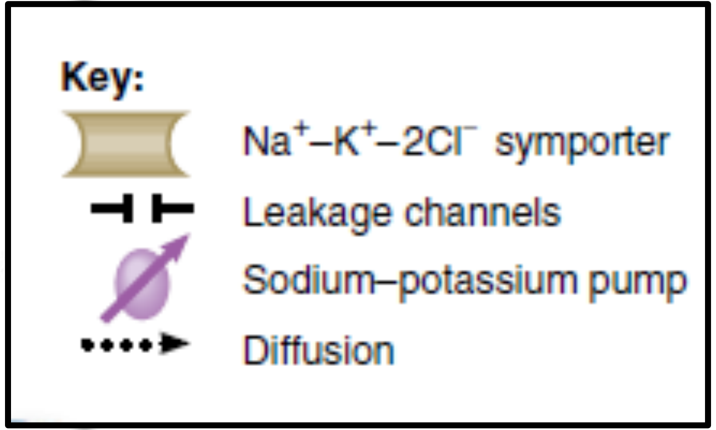
REABSORPTION IN THE NEPHRON LOOP

Because all of the proximal convoluted tubules reabsorb about 65% of the filtered water (about 80 mL/min), fluid enters the next part of the nephron, the nephron loop, at a rate of 40–45 mL/min.

Symporters in the Loop of Henle



- Thick limb of loop of Henle has Na+ K- Cl- symporters that reabsorb these ions
- K+ leaks through K+ channels back into the tubular fluid leaving the interstitial fluid and blood with a negative charge
- Cations passively move to the vasa recta



REABSORPTION IN THE EARLY DISTAL CONVOLUTED TUBULE

- **Fluid enters the distal convoluted tubules at a rate of about 25 mL/ min** because 80% of the filtered water has now been reabsorbed.

- **The early or initial part of the distal convoluted tubule (DCT)** reabsorbs about 10–15% of the filtered water, 5% of the filtered Na ions, and 5% of the filtered Cl ions.

- **Reabsorption of Na and Cl ions** occurs by means of <u>Na–Cl ions symporters in the apical membranes</u>.

REABSORPTION IN THE EARLY DISTAL CONVOLUTED TUBULE

- **Sodium–potassium pumps and Cl ions leakage channels in the basolateral membranes** then permit reabsorption of Na ions and Cl ions into the peritubular capillaries.

- **The early DCT also is a major site where parathyroid hormone (PTH) stimulates reabsorption of calcium ions.** The amount of calcium ions reabsorption in the early DCT varies depending on the body's needs.

Early distal convulated tubules responsible of regulation of Ca

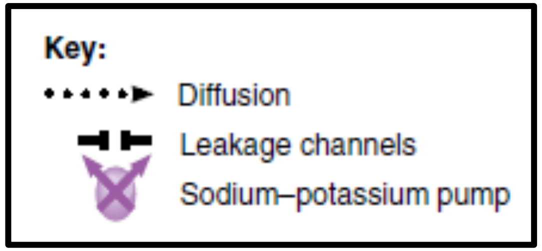
REABSORPTION AND SECRETION IN THE LATE DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

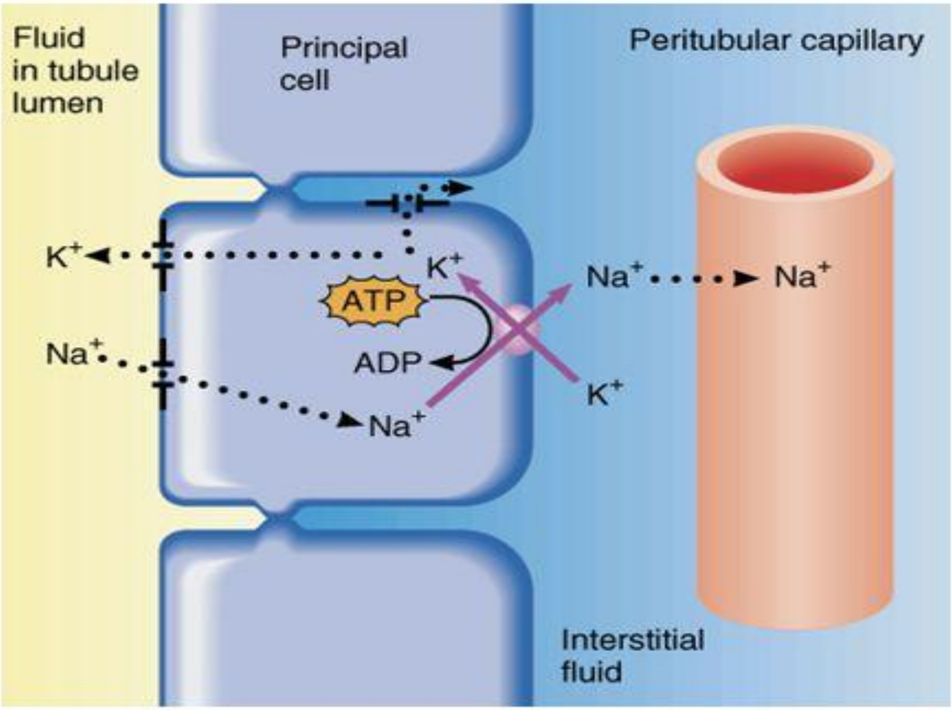
- ✓ **Two different types of cells—principal cells and intercalated cells**—are present at the late or terminal part of the distal convoluted tubule and throughout the collecting duct.

- ✓ **In contrast to earlier segments of the nephron**, sodium ions passes through the apical membrane of principal cells via sodium leakage channels rather than by means of symporters or antiporters.

- ✓ **In the apical membrane of principal cells,** sodium leakage channels allow entry of sodium ions while potassium ions leakage channels allow exit of potassium ions into the tubular fluid.

Actions of the Principal Cells





- Na+ enters principal cells through leakage channels
- Na+ pumps keep the concentration of Na+ in the cytosol low
- Cells secrete variable amounts of K+, to adjust for dietary changes in K+ intake
  - down concentration gradient due to Na+/K+ pump
- Aldosterone increases this Na+ reabsorption (and passive water reabsorption) & K+ secretion by principal cells by stimulating the synthesis of new pumps and channels.

HOMEOSTATIC REGULATION OF TUBULAR REABSORPTION AND TUBULAR SECRETION

- **Five hormones affect the extent of sodium, calcium and chloride ions, and water reabsorption as well as potassium ions secretion by the renal tubules. These hormones include: angiotensin II, aldosterone, antidiuretic hormone, atrial natriuretic peptide, and parathyroid hormone.**

مهم تتأكد أنك فاهم الجدول

TABLE 26.4

Hormonal Regulation of Tubular Reabsorption and Tubular Secretion

HORMONE	MAJOR STIMULI THAT TRIGGER RELEASE	MECHANISM AND SITE OF ACTION	EFFECTS
Angiotensin II	Low blood volume or low blood pressure stimulates renin-induced production of angiotensin II.	Stimulates activity of Na^+–H^+ antiporters in proximal tubule cells.	Increases reabsorption of Na^+, other solutes, and water, which increases blood volume and blood pressure.
Aldosterone	Increased angiotensin II level and increased level of plasma K^+ promote release of aldosterone by adrenal cortex.	Enhances activity of sodium–potassium pumps in basolateral membrane and Na^+ channels in apical membrane of principal cells in collecting duct.	Increases secretion of K^+ and reabsorption of Na^+, Cl^-; increases reabsorption of water, which increases blood volume and blood pressure.
Antidiuretic hormone (ADH)	Increased osmolarity of extracellular fluid or decreased blood volume promotes release of ADH from posterior pituitary gland.	Stimulates insertion of water channel proteins (aquaporin-2) into apical membranes of principal cells.	Increases facultative reabsorption of water, which decreases osmolarity of body fluids.
Atrial natriuretic peptide (ANP)	Stretching of atria of heart stimulates ANP secretion.	Suppresses reabsorption of Na^+ and water in proximal tubule and collecting duct; inhibits secretion of aldosterone and ADH.	Increases excretion of Na^+ in urine (natriuresis); increases urine output (diuresis) and thus decreases blood volume and blood pressure.
Parathyroid hormone (PTH)	Decreased level of plasma Ca^{2+} promotes release of PTH from parathyroid glands.	Stimulates opening of Ca^{2+} channels in apical membranes of early distal tubule cells.	Increases reabsorption of Ca^{2+}.

PRODUCTION OF DILUTE AND CONCENTRATED URINE

- Even though your fluid intake can be highly variable**, the total volume of fluid in your body normally remains stable.**

- Homeostasis of body fluid volume depends in large part on **the ability of the kidneys to regulate the rate of water loss in urine.**

- **Normally functioning kidneys produce a large volume of dilute urine when fluid intake is high, and a small volume of concentrated urine when fluid intake is low or fluid loss is large**.

- **ADH controls whether dilute urine or concentrated urine is formed**. In the absence of ADH, urine is very dilute. However, a high level of ADH stimulates reabsorption of more water into blood, producing a concentrated urine.

استهلاك كميات كبيرة من الماء ← ADH قليل ← large volume of dilute urine

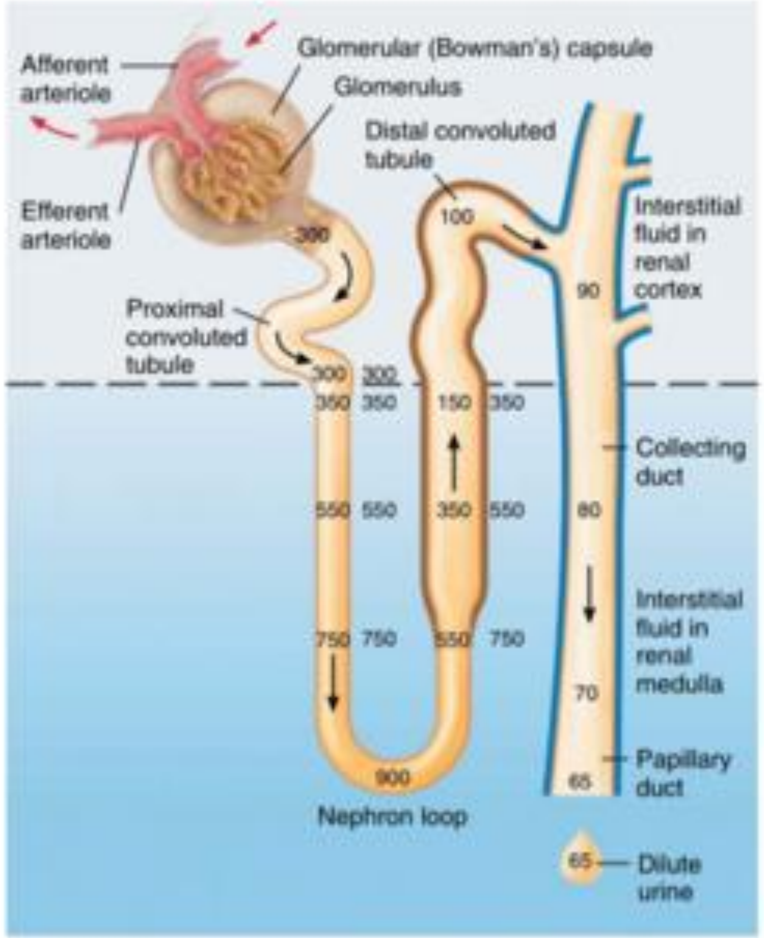
استهلاك كميات قليلة من الماء ← ADH عالي ← small volume of concentrated urine

concentrated urine ← لونه غامق

dilute urine ← لونه فاتح

Figure 26.18 Formation of dilute urine. Numbers indicate osmolarity in milliosmoles per liter (mOsm/liter). Heavy brown lines in the ascending limb of the nephron loop and in the distal convoluted tubule indicate impermeability to water; heavy blue lines indicate the last part of the distal convoluted tubule and the collecting duct, which are impermeable to water in the absence of ADH; light blue areas around the nephron represent interstitial fluid.

When the ADH level is low, urine is dilute and has an osmolarity less than the osmolarity of blood.



FORMATION OF DILUTE URINE

- **Glomerular filtrate has the same ratio of water and solute particles as blood**; its osmolarity is about 300 mOsm/liter.
- **Fluid leaving the proximal convoluted tubule is still isotonic to plasma**.
- When dilute urine is being formed, the osmolarity of the fluid in the tubular lumen increases as it flows down the descending limb of the nephron loop, decreases as it flows up the ascending limb, and decreases still more as it flows through the rest of the nephron and collecting duct.

Figure 26.18 Formation of dilute urine. Numbers indicate osmolarity in milliosmoles per liter (mOsm/liter). Heavy brown lines in the ascending limb of the nephron loop and in the distal convoluted tubule indicate impermeability to water; heavy blue lines indicate the last part of the distal convoluted tubule and the collecting duct, which are impermeable to water in the absence of ADH; light blue areas around the nephron represent interstitial fluid.

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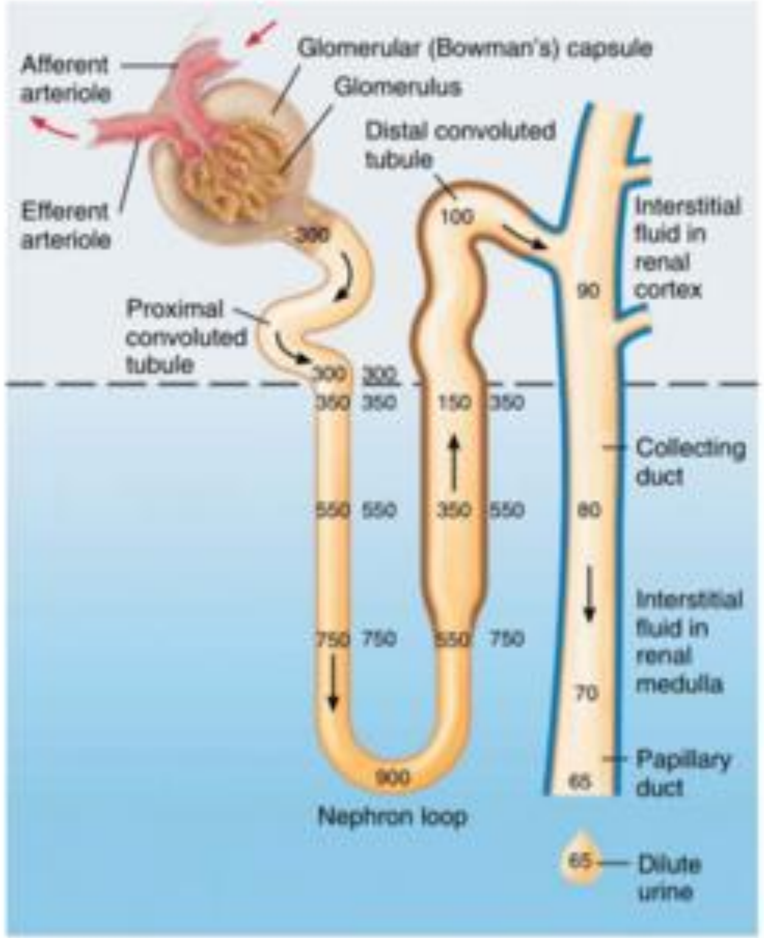

FORMATION OF DILUTE URINE

1. Because the **osmolarity of the interstitial fluid of the renal medulla becomes progressively greater,** more and more water is reabsorbed by osmosis as tubular fluid flows along the descending limb toward the tip of the nephron loop.

2. Cells lining the thick ascending limb of the loop have symporters that actively reabsorb sodium, potassium, and chloride ions from the tubular fluid.

Figure 26.18 Formation of dilute urine. Numbers indicate osmolarity in milliosmoles per liter (mOsm/liter). Heavy brown lines in the ascending limb of the nephron loop and in the distal convoluted tubule indicate impermeability to water; heavy blue lines indicate the last part of the distal convoluted tubule and the collecting duct, which are impermeable to water in the absence of ADH; light blue areas around the nephron represent interstitial fluid.

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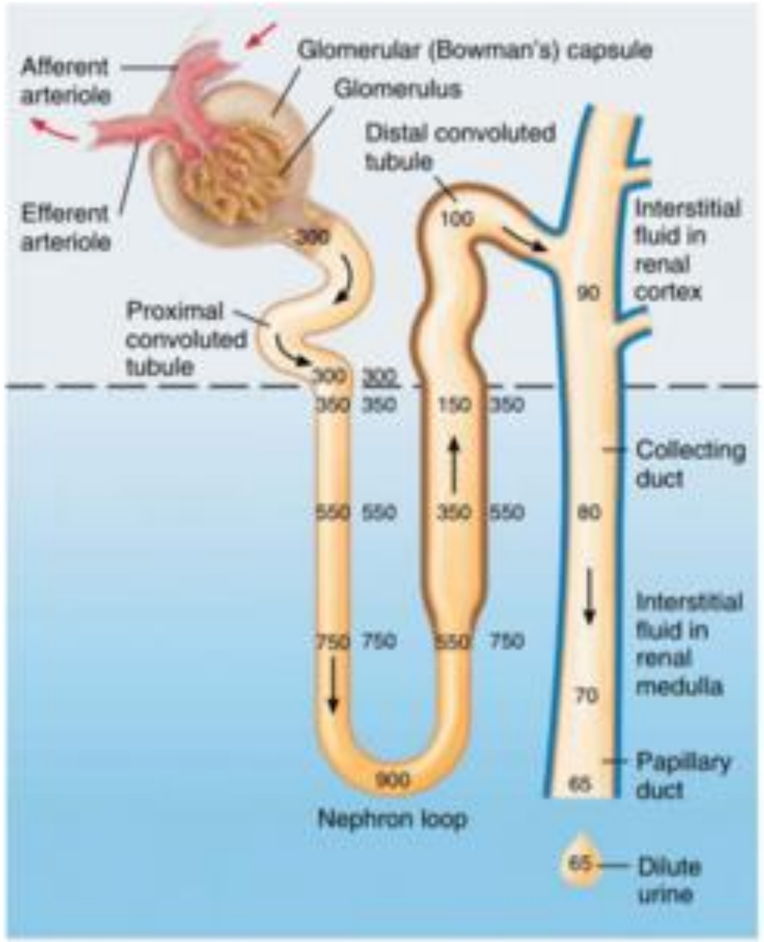

FORMATION OF DILUTE URINE

2. The ions pass from the tubular fluid into thick ascending limb cells, then into interstitial fluid, and finally some diffuse into the blood inside the vasa recta.

3. Although solutes are being reabsorbed in the thick ascending limb, the water permeability of this portion of the nephron is always quite low, so water cannot follow by osmosis. As solutes—but not water molecules—are leaving the tubular fluid, its osmolarity drops to about 150 mOsm/liter. The fluid entering the distal convoluted tubule is thus more dilute than plasma.

Figure 26.18 Formation of dilute urine. Numbers indicate osmolarity in milliosmoles per liter (mOsm/liter). Heavy brown lines in the ascending limb of the nephron loop and in the distal convoluted tubule indicate impermeability to water; heavy blue lines indicate the last part of the distal convoluted tubule and the collecting duct, which are impermeable to water in the absence of ADH; light blue areas around the nephron represent interstitial fluid.

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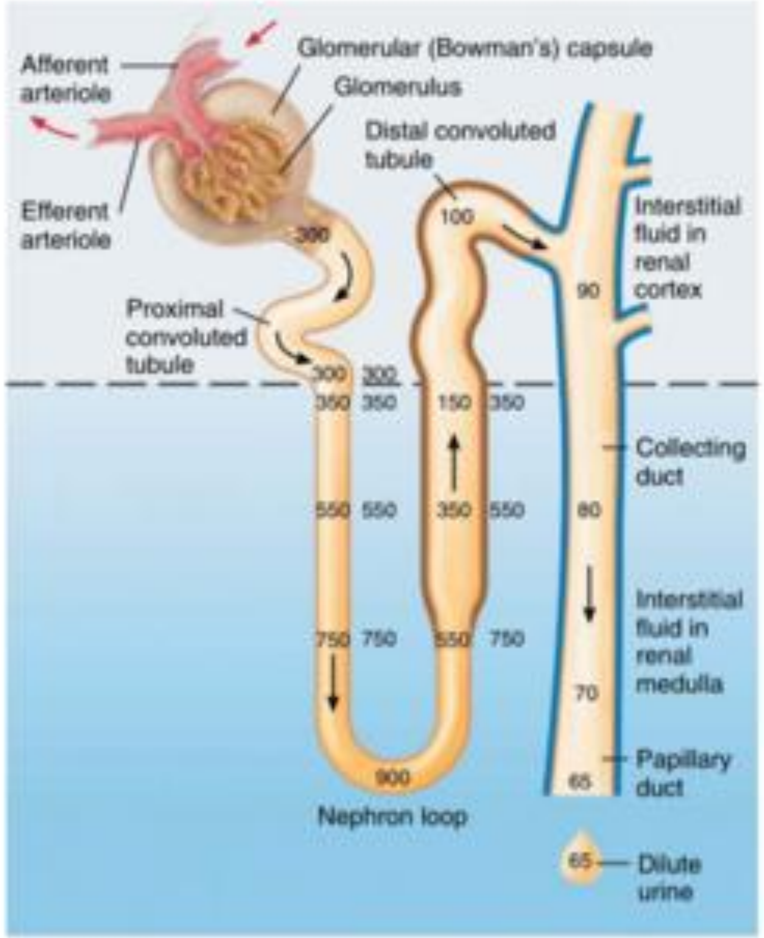


FORMATION OF DILUTE URINE

4. While the fluid continues flowing along the distal convoluted tubule, additional solutes but only a few water molecules are reabsorbed. The early distal convoluted tubule cells are not very permeable to water and are not regulated by ADH.

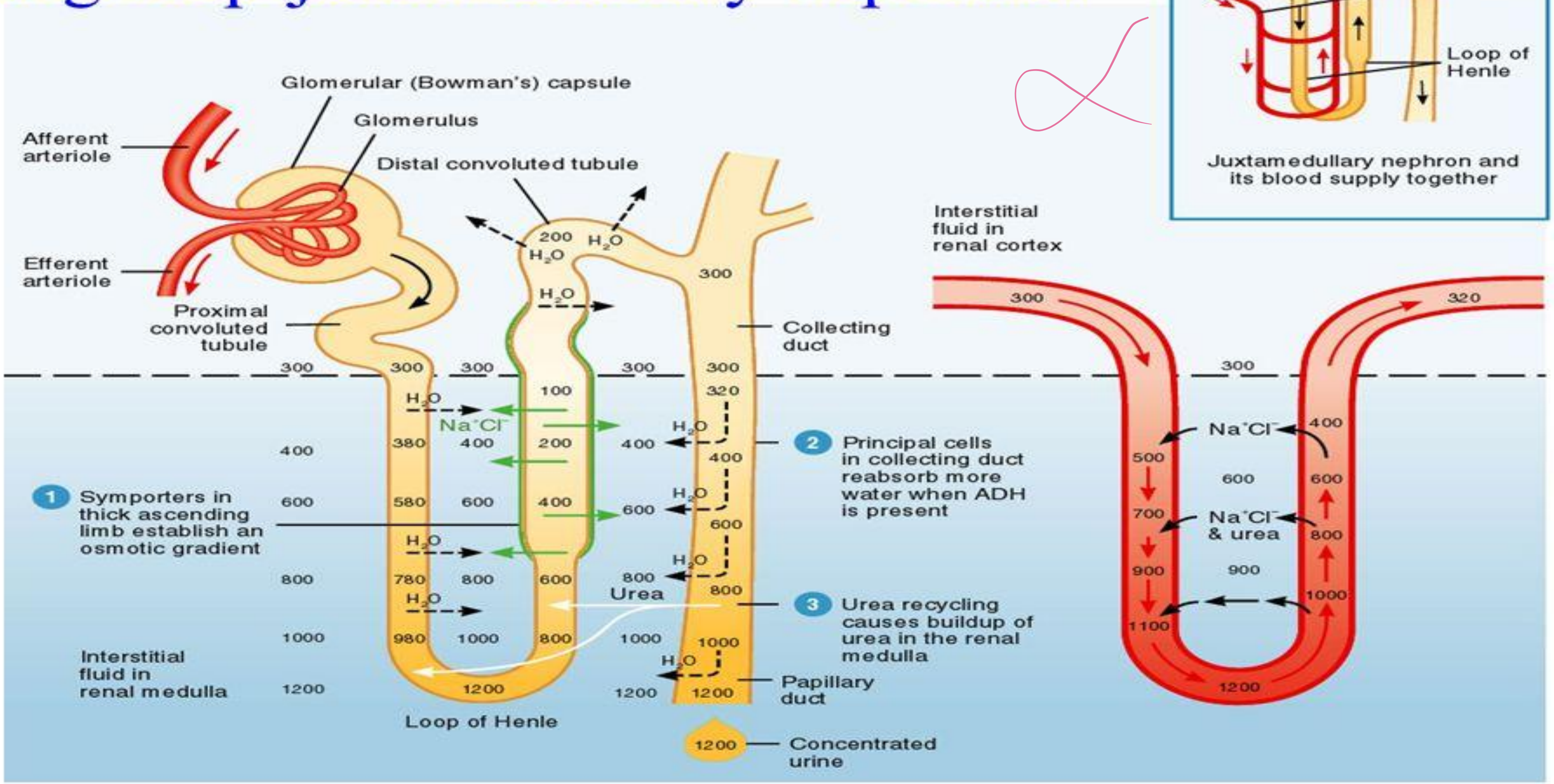
5. Finally, the principal cells of the late distal convoluted tubules and collecting ducts are impermeable to water when the ADH level is very low. Thus, tubular fluid becomes progressively more dilute as it flows onward. By the time the tubular fluid drains into the renal pelvis, its concentration can be as low as 65–70 mOsm/liter. This is four times more dilute than blood plasma or glomerular filtrate.

FORMATION OF CONCENTRATED URINE

- **When water intake is low or water loss is high** (such as during heavy sweating), **the kidneys must conserve water while still eliminating wastes and excess ions.** Under the influence of ADH, the kidneys produce a small volume of highly concentrated urine.

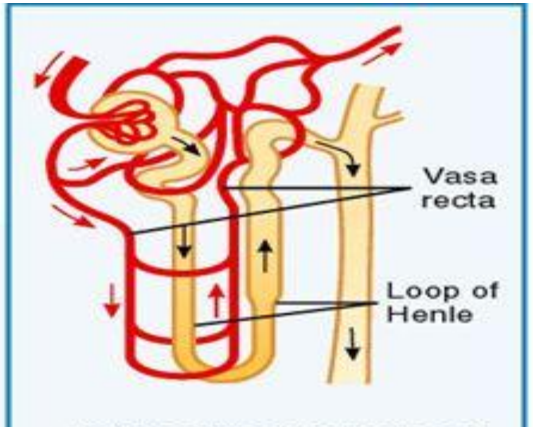
- <u>Urine can be four times more concentrated (up to 1200 mOsm/liter) than blood plasma or glomerular filtrate (300 mOsm/liter).</u>

Mechanism of urine concentration in long-loop juxtamedullary nephrons



(a) Reabsorption of Na^+, Cl^- and water in a long-loop juxtamedullary nephron

(b) Recycling of salts and urea in the vasa recta



Juxtamedullary nephron and its blood supply together

FORMATION OF CONCENTRATED URINE

- The ability of **ADH** to cause excretion of concentrated urine **depends on the presence of an osmotic gradient of solutes in the interstitial fluid of the renal medulla.**

- **Two main factors contribute to building and maintaining this osmotic gradient:** (1) differences in solute and water permeability and reabsorption in different sections of the long nephron loops and the collecting ducts, and (2) the countercurrent flow of fluid through tube-shaped structures in the renal medulla.

FORMATION OF CONCENTRATED URINE

- **Countercurrent flow refers to the flow of fluid in opposite directions.** This occurs when fluid flowing in one tube runs counter (opposite) to fluid flowing in a nearby parallel tube. Examples of countercurrent flow include the flow of tubular fluid through the descending and ascending limbs of the nephron loop and the flow of blood through the ascending and descending parts of the vasa recta.

FORMATION OF CONCENTRATED URINE

- **Since countercurrent flow through the descending and ascending limbs of the long nephron** loop **establishes the osmotic gradient in the renal medulla**, the long nephron loop is said to function as a countercurrent multiplier. **The kidneys use this osmotic gradient to excrete concentrated urine**.

FORMATION OF CONCENTRATED URINE

- **Production of concentrated urine by the kidneys occurs in the following way:**

1. **Symporters in thick ascending limb cells** of the nephron loop cause a buildup of Na and Cl ions in the renal medulla (water is not reabsorbed in this segment).

2. **Countercurrent flow through the descending and ascending limbs of the nephron loop** establishes an osmotic gradient in the renal medulla.

FORMATION OF CONCENTRATED URINE

2. <u>**Countercurrent flow**</u>: **Since tubular fluid constantly moves from the descending limb to the thick ascending limb of the nephron loop, the thick ascending limb is constantly reabsorbing Na and Cl ions.** **Consequently, the reabsorbed Na and Cl ions become increasingly concentrated in the interstitial fluid of the medulla, which results in the formation of an osmotic gradient.**

FORMATION OF CONCENTRATED URINE

- **The descending limb of the nephron loop is very permeable to water but impermeable to solutes except urea.**

- **Because the osmolarity of the interstitial fluid outside the descending limb is higher than the tubular fluid within it, water moves out of the descending limb via osmosis.**

FORMATION OF CONCENTRATED URINE

❖ The ascending limb of the loop is impermeable to water, but its symporters reabsorb Na and Cl ions from the tubular fluid into the interstitial fluid of the renal medulla, so the osmolarity of the tubular fluid progressively decreases as it flows through the ascending limb. Overall, tubular fluid becomes progressively more concentrated as it flows along the descending limb and progressively more dilute as it moves along the ascending limb.

FORMATION OF CONCENTRATED URINE

3. **Cells in the collecting ducts reabsorb more water and urea.** When ADH increases the water permeability of the principal cells, water quickly moves via osmosis out of the collecting duct tubular fluid, into the interstitial fluid of the inner medulla, and then into the vasa recta.

FORMATION OF CONCENTRATED URINE

4. **Urea recycling** causes a buildup of urea in the renal medulla.

- As urea accumulates in the interstitial fluid, some of it diffuses into the tubular fluid in the **descending and thin ascending limbs of the long nephron loops,** which also are **permeable to urea.**

- However, while the fluid flows through the **thick ascending limb, distal convoluted tubule, and cortical portion of the collecting duct, urea remains in the lumen because cells in these segments are impermeable to it.**

- **As fluid flows along the collecting ducts, water reabsorption continues via osmosis because ADH is present.**

Figure 26.20 Summary of filtration, reabsorption, and secretion in the nephron and collecting duct.

Filtration occurs in the renal corpuscle; reabsorption occurs all along the renal tubule and collecting ducts.

PROXIMAL CONVOLUTED TUBULE

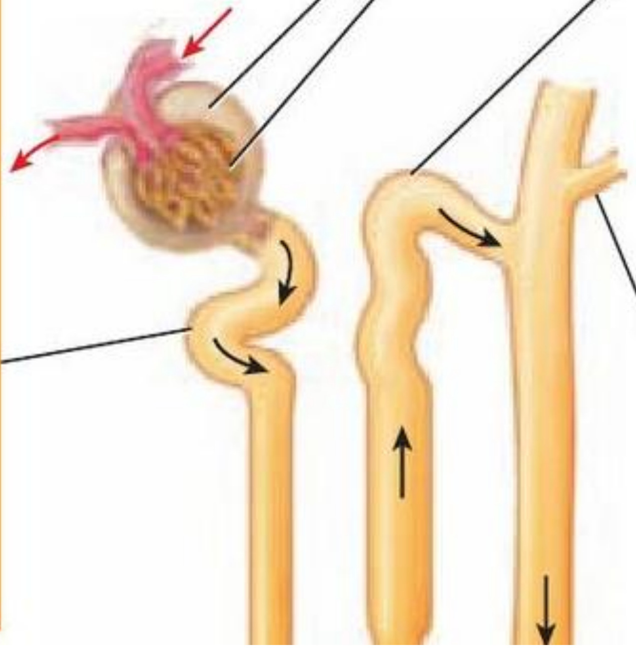
Reabsorption (into blood) of filtered:

Water	65% (osmosis)
Na^+	65% (sodium–potassium pumps, symporters, antiporters)
K^+	65% (diffusion)
Glucose	100% (symporters and facilitated diffusion)
Amino acids	100% (symporters and facilitated diffusion)
Cl^-	50% (diffusion)
HCO_3^-	80–90% (facilitated diffusion)
Urea	50% (diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

H^+	variable (antiporters)
NH_4^+	variable, increases in acidosis (antiporters)
Urea	variable (diffusion)
Creatinine	small amount

At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).



RENAL CORPUSCLE

Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood

Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid

EARLY DISTAL CONVOLUTED TUBULE

Reabsorption (into blood) of:

Water	10–15% (osmosis)
Na^+	5% (symporters)
Cl^-	5% (symporters)
Ca^{2+}	variable (stimulated by parathyroid hormone)

LATE DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

Reabsorption (into blood) of:

Water	5–9% (insertion of water channels stimulated by ADH)
Na^+	1–4% (sodium–potassium

isotonic to blood (300 mOsm/liter).

LOOP OF HENLE

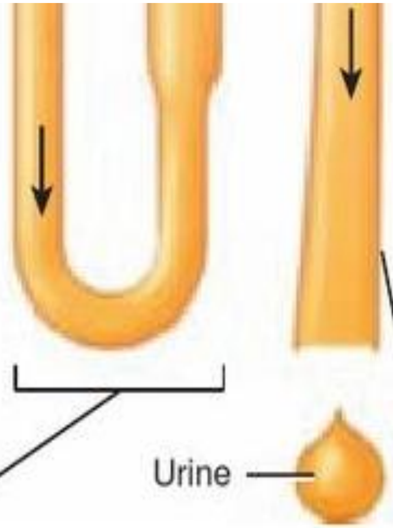
Reabsorption (into blood) of:

Water	15% (osmosis in descending limb)
Na^+	20–30% (symporters in ascending limb)
K^+	20–30% (symporters in ascending limb)
Cl^-	35% (symporters in ascending limb)
HCO_3^-	10–20% (facilitated diffusion)
Ca^{2+}, Mg^{2+}	variable (diffusion)

Secretion (into urine) of:

Urea	variable (recycling from collecting duct)

At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).



	ADH)
Na^+	1–4% (sodium–potassium pumps and sodium channels stimulated by aldosterone)
HCO_3^-	variable amount, depends on H^+ secretion (antiporters)
Urea	variable (recycling to loop of Henle)

Secretion (into urine) of:

K^+	variable amount to adjust for dietary intake (leakage channels)
H^+	variable amounts to maintain acid–base homeostasis (H^+ pumps)

Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.

EVALUATION OF KIDNEY FUNCTION:

شفاف أو غير شفاف

1- URINALYSIS

TABLE 26.5

Characteristics of Normal Urine

CHARACTERISTIC	DESCRIPTION
Volume	One to two liters in 24 hours; varies considerably.
Color	Yellow or amber; varies with urine concentration and diet. Color due to urochrome (pigment produced from breakdown of bile) and urobilin (from breakdown of hemoglobin). Concentrated urine is darker in color. Color affected by diet (reddish from beets), medications, and certain diseases. Kidney stones may produce blood in urine. العصارة الصفراوية يصبح لون urine أحمر من الشمندر
Turbidity	Transparent when freshly voided; becomes turbid (cloudy) on standing. معكّر
Odor	Mildly aromatic; becomes ammonia-like on standing. Some people inherit ability to form methylmercaptan from digested asparagus, which gives characteristic odor. Urine of diabetics has fruity odor due to presence of ketone bodies. أكل الهيليون قد يغير رائحة urine للي معهم سكري بتكون رائحة urine تشبه الفواكه
pH	Ranges between 4.6 and 8.0; average 6.0; varies considerably with diet. High-protein diets increase acidity; vegetarian diets increase alkalinity.
Specific gravity (density)	Specific gravity (density) is ratio of weight of volume of substance to weight of equal volume of distilled water. In urine, 1.001–1.035. The higher the concentration of solutes, the higher the specific gravity.

TABLE 26.6

Summary of Abnormal Constituents in Urine

ABNORMAL CONSTITUENT	COMMENTS
Albumin	Normal constituent of plasma; usually appears in only very small amounts in urine because it is too large to pass through capillary fenestrations. Presence of excessive albumin in urine—**albuminuria** (al′-bū-mi-NOO-rē-a)—indicates increase in permeability of filtration membranes due to injury or disease, increased blood pressure, or irritation of kidney cells by substances such as bacterial toxins, ether, or heavy metals.
Glucose	Presence of glucose in urine—**glucosuria** (gloo-kō-SOO-rē-a)—usually indicates diabetes mellitus. Occasionally caused by stress, which can cause excessive epinephrine secretion. Epinephrine stimulates breakdown of glycogen and liberation of glucose from liver.
Red blood cells (erythrocytes)	Presence of red blood cells in urine—**hematuria** (hēm-a-TOO-rē-a)—generally indicates pathological condition. One cause is acute inflammation of urinary organs due to disease or irritation from kidney stones. Other causes: tumors, trauma, kidney disease, contamination of sample by menstrual blood.
Ketone bodies	High levels of ketone bodies in urine—**ketonuria** (kē-tō-NOO-rē-a)—may indicate diabetes mellitus, anorexia, starvation, or too little carbohydrate in diet.

TABLE 26.6

Summary of Abnormal Constituents in Urine

ABNORMAL CONSTITUENT	COMMENTS
Bilirubin	When red blood cells are destroyed by macrophages, the globin portion of hemoglobin is split off and heme is converted to biliverdin. Most biliverdin is converted to bilirubin, which gives bile its major pigmentation. Above-normal level of bilirubin in urine is called **bilirubinuria** (bil′-ē-roo-bi-NOO-rē-a).
Urobilinogen	Presence of urobilinogen (breakdown product of hemoglobin) in urine is called **urobilinogenuria** (ū′-rō-bi-lin′-ō-je-NOO-rē-a). Trace amounts are normal, but elevated urobilinogen may be due to hemolytic or pernicious anemia, infectious hepatitis, biliary obstruction, jaundice, cirrhosis, congestive heart failure, or infectious mononucleosis.
Casts	Casts are tiny masses of material that have hardened and assumed shape of lumen of tubule in which they formed, from which they are flushed when filtrate builds up behind them. Casts are named after cells or substances that compose them or based on appearance (for example, white blood cell casts, red blood cell casts, and epithelial cell casts that contain cells from walls of tubules).
Microbes	Number and type of bacteria vary with specific urinary tract infections. One of the most common is *E. coli*. Most common fungus is yeast *Candida albicans*, cause of vaginitis. Most frequent protozoan is *Trichomonas vaginalis*, cause of vaginitis in females and urethritis in males.

EVALUATION OF KIDNEY FUNCTION:
2- BLOOD TESTS

- **Two blood-screening tests can provide information about kidney function:-**

1. **Blood urea nitrogen (BUN) test.**
2. **Plasma creatinine.**

BLOOD UREA NITROGEN (BUN) TEST

- **It measures the blood nitrogen that is part of the urea resulting from catabolism and deamination of amino acids.**

- **When glomerular filtration rate decreases severely**, as may occur with renal disease or obstruction of the urinary tract, **BUN rises steeply.** لے لأن urea المفروض يحدث لها secreation بالتالي عدم خروجها مؤشر على وجود مشكلة بالكلى
-
- **One strategy in treating such patients is to minimize their protein intake**, thereby reducing the rate of urea production.

PLASMA CREATININE

- **It results from catabolism of creatine phosphate in skeletal muscle.**

- **Normally, the blood creatinine level remains steady because the rate of creatinine excretion in the urine equals its discharge from muscle.** معدل الكرياتنين في الجسم الطبيعي يكون ثابت في الدم لأنو معدل إنتاجه في العضلات يساوي معدل التخلص منه في الكلى

- **A creatinine level above 1.5 mg/dL (135 mmol/liter) usually is an indication of poor renal function.**

RENAL PLASMA CLEARANCE

- **Renal plasma clearance** is the volume of blood that is "cleaned" or cleared of a substance per unit of time, usually expressed in **units of milliliters per minute.**

الإخراج غير كافي

- ***Low clearance*** **indicates** ***inefficient excretion*****. For example, the clearance of glucose normally is zero because it is completely reabsorbed; therefore, glucose is not excreted at all.**

RENAL PLASMA CLEARANCE

❖ **Knowing a drug's clearance is essential for determining the correct dosage. If clearance is high (one example is penicillin), then the dosage must also be high, and the drug must be given several times a day to maintain an adequate therapeutic level in the blood.**

The following equation is used to calculate clearance:

$$\text{Renal plasma clearance of substance S} = \left(\frac{U \times V}{P}\right)$$

where U and P are the concentrations of the substance in urine and plasma, respectively (both expressed in the same units, such as mg/mL), and V is the urine flow rate in mL/min.

RENAL PLASMA CLEARANCE

- **The clearance of a solute depends on the three basic processes of a nephron:**

1. **Glomerular filtration.**
2. **Tubular reabsorption.**
3. **Tubular secretion.**

TABLE 26.7

Summary of Urinary System Organs

STRUCTURE	LOCATION	DESCRIPTION	FUNCTION
Kidneys	Posterior abdomen between last thoracic and third lumbar vertebrae posterior to peritoneum (retroperitoneal). Lie against ribs 11 and 12.	Solid, reddish, bean-shaped organs. Internal structure: three tubular systems (arteries, veins, urinary tubes).	Regulate blood volume and composition, help regulate blood pressure, synthesize glucose, release erythropoietin, participate in vitamin D synthesis, excrete wastes in urine.
Ureters	Posterior to peritoneum (retroperitoneal); descend from kidney to urinary bladder along anterior surface of psoas major muscle and cross back of pelvis to reach inferoposterior surface of urinary bladder anterior to sacrum.	Thick, muscular walled tubes with three structural layers: mucosa of transitional epithelium, muscularis with circular and longitudinal layers of smooth muscle, adventitia of areolar connective tissue.	Transport tubes that move urine from kidneys to urinary bladder.
Urinary bladder	In pelvic cavity anterior to sacrum and rectum in males and sacrum, rectum, and vagina in females and posterior to pubis in both sexes. In males, superior surface covered with parietal peritoneum; in females, uterus covers superior aspect.	Hollow, distensible, muscular organ with variable shape depending on how much urine it contains. Three basic layers: inner mucosa of transitional epithelium, middle smooth muscle coat (detrusor muscle), outer adventitia or serosa over superior aspect in males.	Storage organ that temporarily stores urine until convenient to discharge from body.
Urethra	Exits urinary bladder in both sexes. In females, runs through perineal floor of pelvis to exit between labia minora. In males, passes through prostate, then perineal floor of pelvis, and then penis to exit at its tip.	Thin-walled tubes with three structural layers: inner mucosa that consists of transitional, stratified columnar, and stratified squamous epithelium; thin middle layer of circular smooth muscle; thin connective tissue exterior.	Drainage tube that transports stored urine from body.

THANK YOU

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