Physiology

Physiology of the Kidneys

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Kidney Function

- Regulate ECF (plasma and interstitial fluid) through formation of urine.
  - Primary function.
- Regulate volume of blood plasma.
  - BP.
- Regulate [waste products] in the blood.
- Regulate concentration of electrolytes.
  - Na^+, K^+, and HCO_3^- and other ions.
- Regulate pH.
- Secrete erythropoietin.

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Structure of the Kidney

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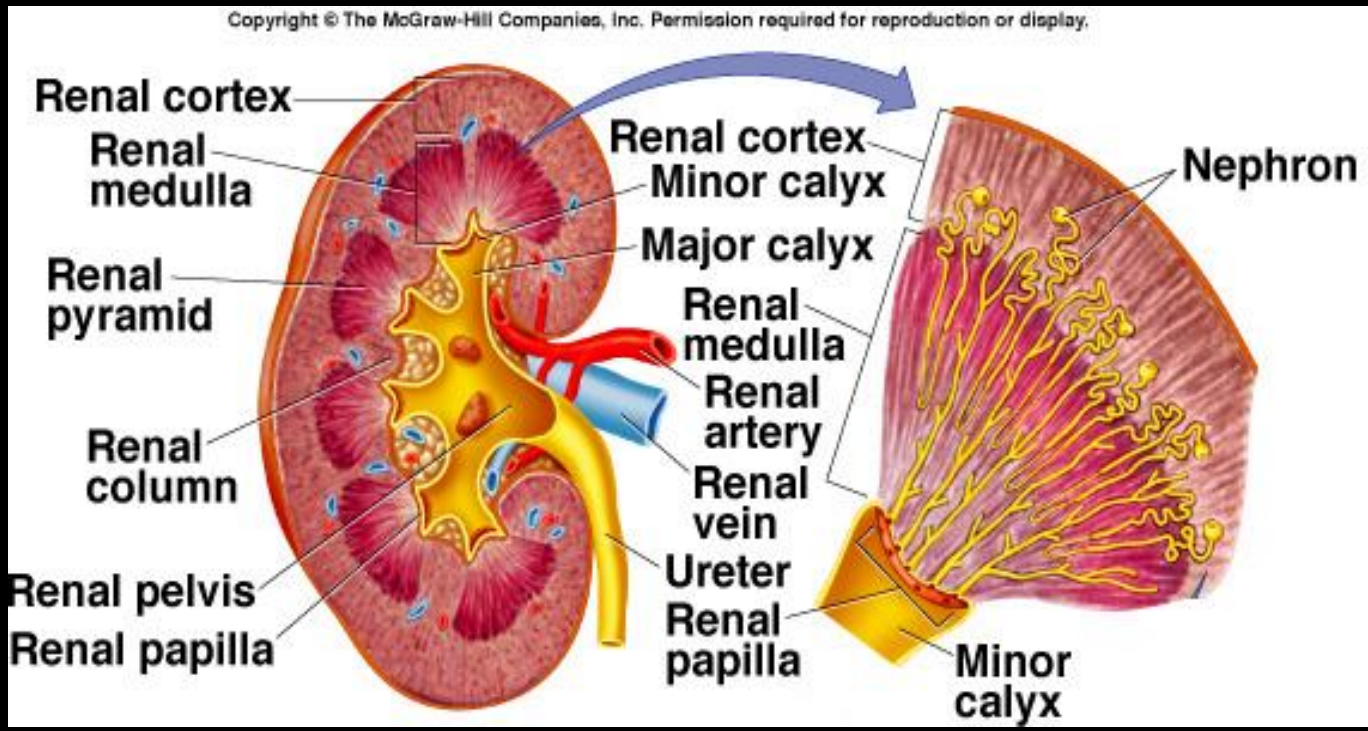
- Outer cortex:
  - Contains many capillaries.
- Medulla:
  - Renal pyramids separated by renal columns.
  - Pyramid contains minor calyces which unite to form a major calyx.



- Major calyces form renal pelvis.
- Renal pelvis collects urine.
- Transports urine to ureters.

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Micturition Reflex

- Actions of the internal urethral sphincter and the external urethral sphincter are regulated by reflex control center located in the spinal cord.
  - Filling of the urinary bladder activates the stretch receptors, that send impulses to the micturition center.
    - Activates parasympathetic neurons, causing rhythmic contraction of the detrusor muscle and relaxation of the internal urethral sphincter.
  - Voluntary control over the external urethral sphincter.
- When urination occurs, descending motor tracts to the micturition center inhibit somatic motor fibers of the external urethral sphincter.

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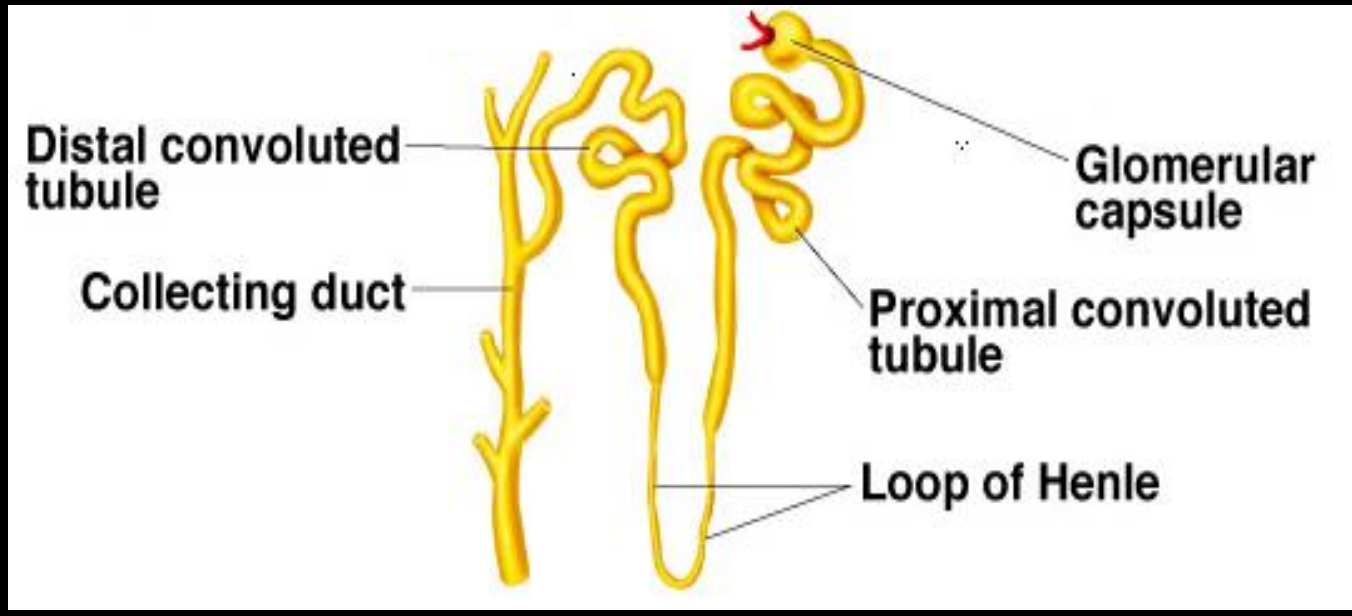
Nephron

- Functional unit of the kidney.
- Consists of:
  - Blood vessels:
    - Vasa recta.
    - Peritubular capillaries.
  - Urinary tubules:
    - PCT.
    - LH.
    - DCT.
    - CD.



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Renal Blood Vessels

- Afferent arteriole:
  - Delivers blood into the glomeruli.
- Glomeruli:
  - Capillary network that produces filtrate that enters the urinary tubules.
- Efferent arteriole:
  - Delivers blood from glomeruli to peritubular capillaries.
- Peritubular capillaries:
  - Deliver blood to vasa recta.

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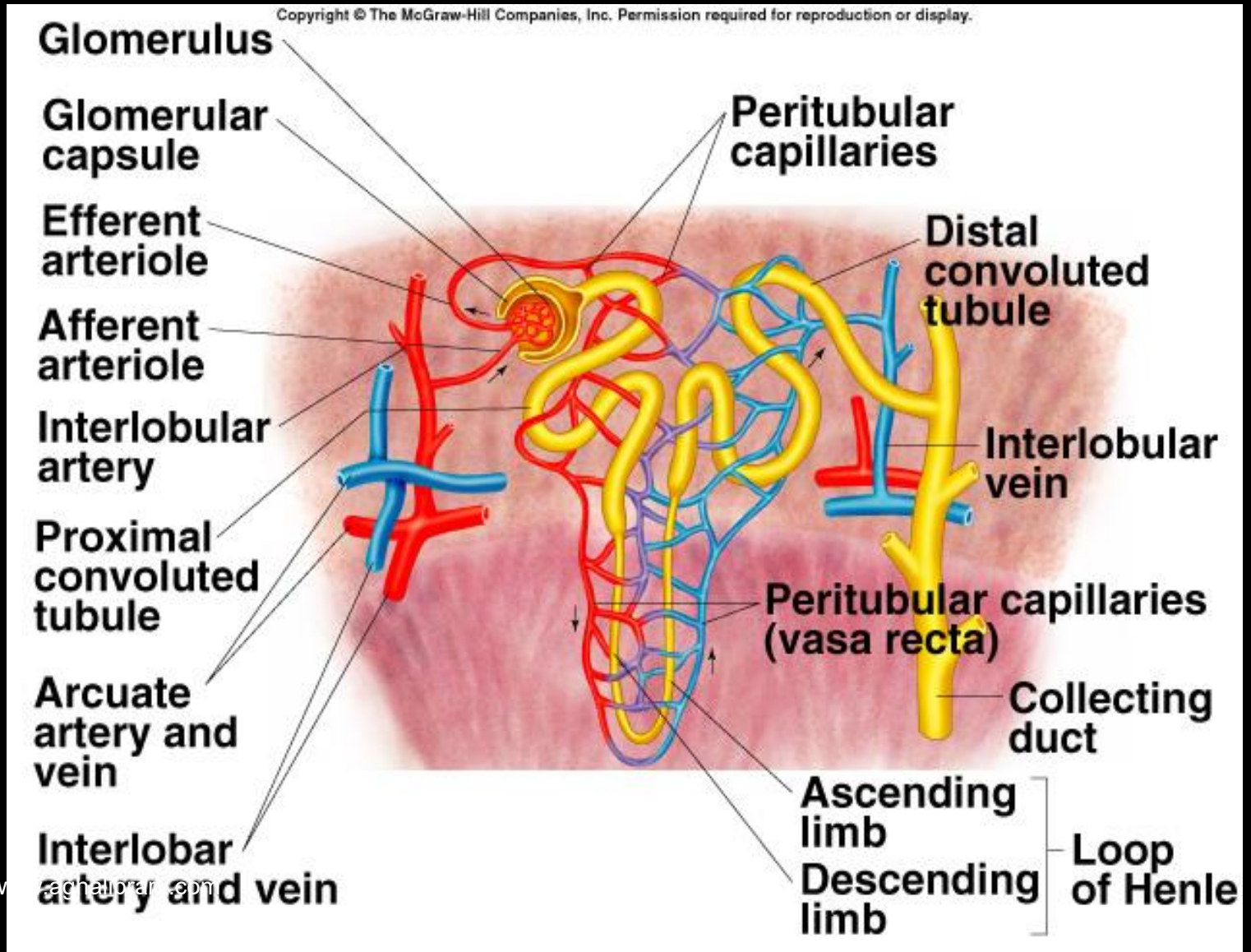
Renal Blood Vessels (continued)



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Nephron Tubules

- Glomerular capsule.
- Proximal convoluted tubule (PCT).
- Descending and ascending limbs of Loop of Henle (LH).
- Distal convoluted tubule (DCT).
- Collecting duct (CD).

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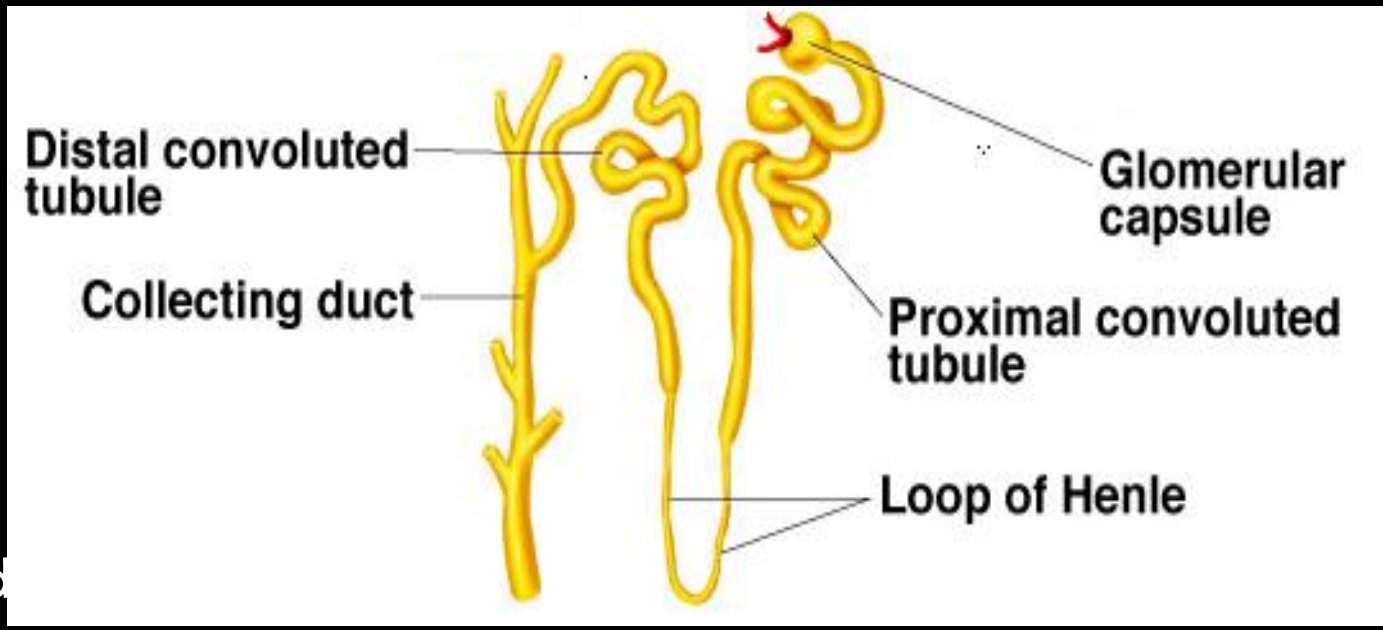

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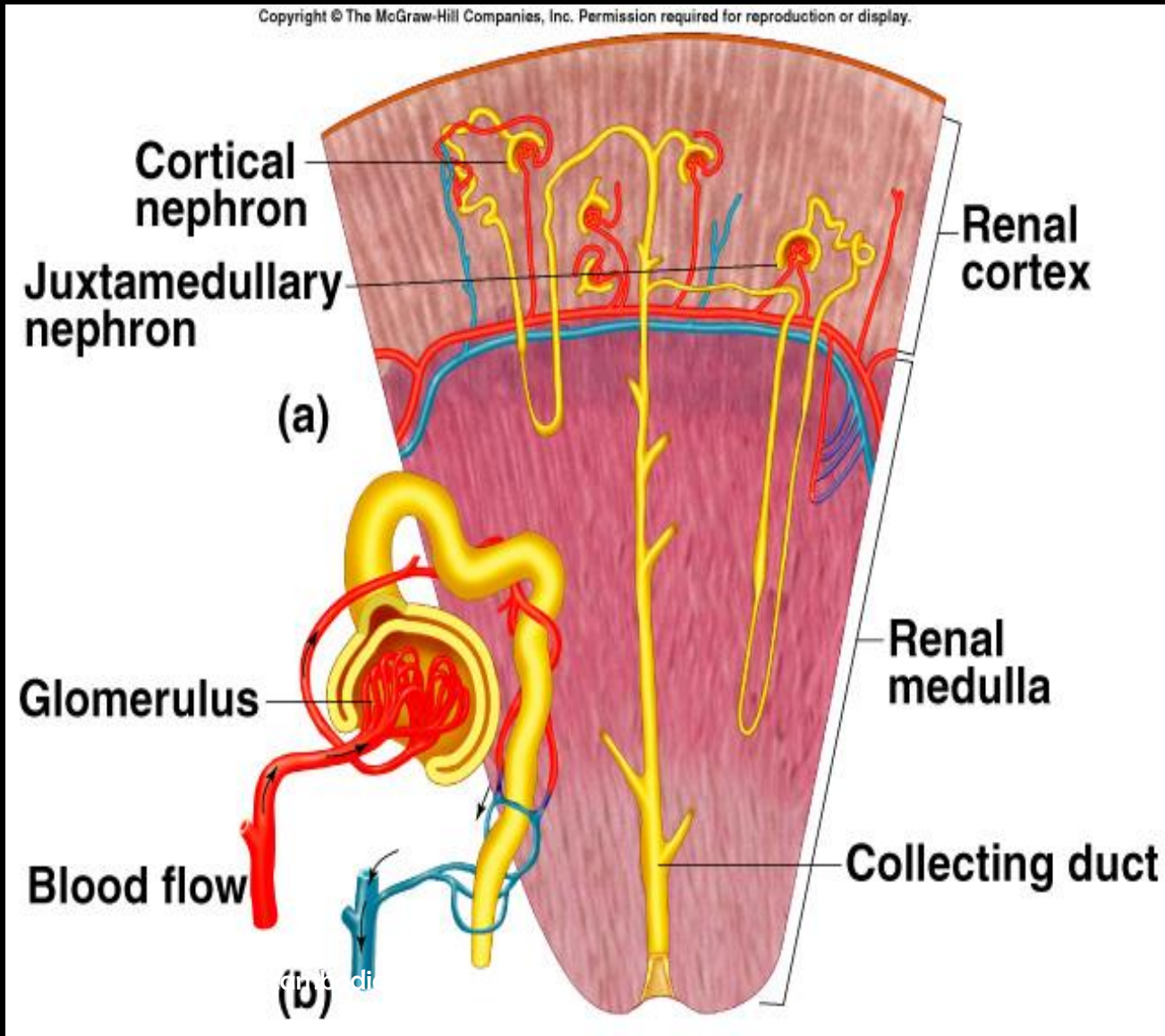
Glomerular Capsule

- Bowman's capsule:
  - Surrounds the glomerulus.
    - Location where glomerular filtration occurs.
- Filtrate passes into the urinary space into PCT.



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Proximal Convoluted Tubule

- Single layer of cuboidal cells with millions of microvilli.
  - Increase surface area for reabsorption.
- PCT functions:
  - Reabsorption.
  - Secretion.

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Loop of Henle

- Fluid passes from PCT to LH.
- Descending limb:
  - H_2O reabsorption.
- Ascending limb:
  - Active transport of Na^+.
  - Impermeable to H_2O.

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Distal Convoluted Tubule

- Contains few microvilli.
- Functions:
  - Secretion.
  - Reabsorption.
- Terminates in CD.

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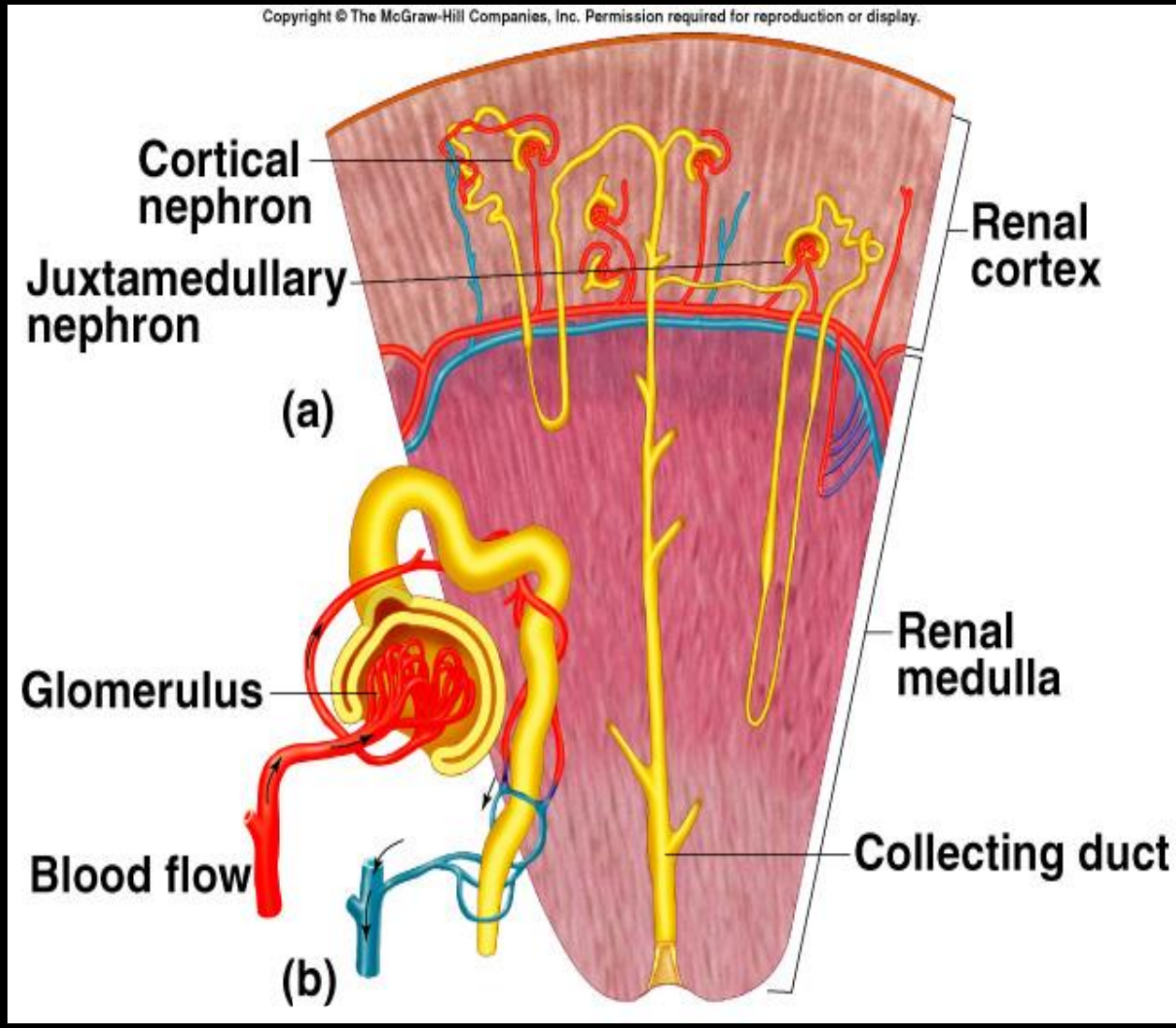
Type of Nephrons

- Cortical nephron:
  - Originates in outer 2/3 of cortex.
    - Osmolarity of 300 mOsm/l.
  - Involved in solute reabsorption.
- Juxtamedullary nephron:
  - Originates in inner 1/3 cortex.
    - Important in the ability to produce a concentrated urine.
  - Has longer LH.



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Collecting Duct

- Receives fluid from the DCT of several nephrons.
- Passes through renal pyramid into minor calyx.
- Functions:
  - Reabsorption.
    - H_2O reabsorption influenced by ADH.
  - Secretion.

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Glomerular Filtration Membrane

- Endothelial capillary pores are large fenestrae.
- 100-400 times more permeable to plasma, H_2O, and dissolved solutes than capillaries of skeletal muscles.
- Pores are small enough to prevent RBCs, platelets, and WBCs from passing through the pores.

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Glomerular Filtration Membrane (continued)

- Filtrate must pass through the basement membrane:
  - Thin glycoprotein layer.
  - Negatively charged.
- Podocytes:
  - Foot pedicels form small filtration slits.
  - Passageway through which filtered molecules must pass.

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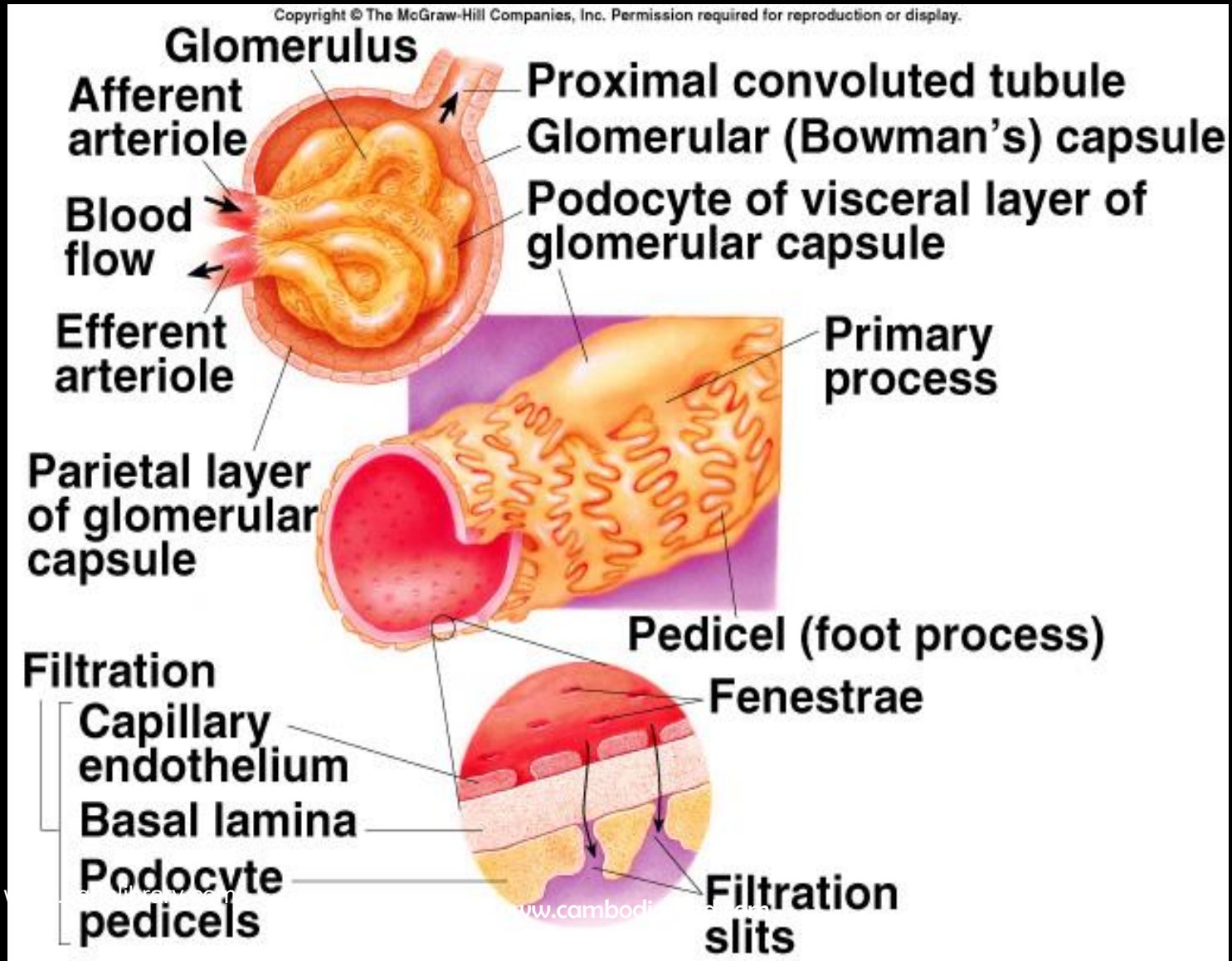
Glomerular Filtration Membrane (continued)



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Glomerular Ultrafiltrate

- Fluid that enters glomerular capsule is called ultrafiltrate.
  - Glomerular filtration:
    - Mechanism of producing ultrafiltrate under hydrostatic pressure of the blood.
      - Process similar to the formation of tissue fluid by other capillary beds.
- Glomerular filtration rate (GFR):
  - Volume of filtrate produced by both kidneys each minute.
    - Averages 115 ml/min. in women; 125 ml/min. in men.

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Regulation of GFR

- Vasoconstriction or dilation of the afferent arterioles affects the rate of blood flow to the glomerulus.
  - Affects GFR.
- Mechanisms to regulate GFR:
  - Sympathetic nervous system.
  - Autoregulation.
- Changes in diameter result from extrinsic and intrinsic mechanisms.

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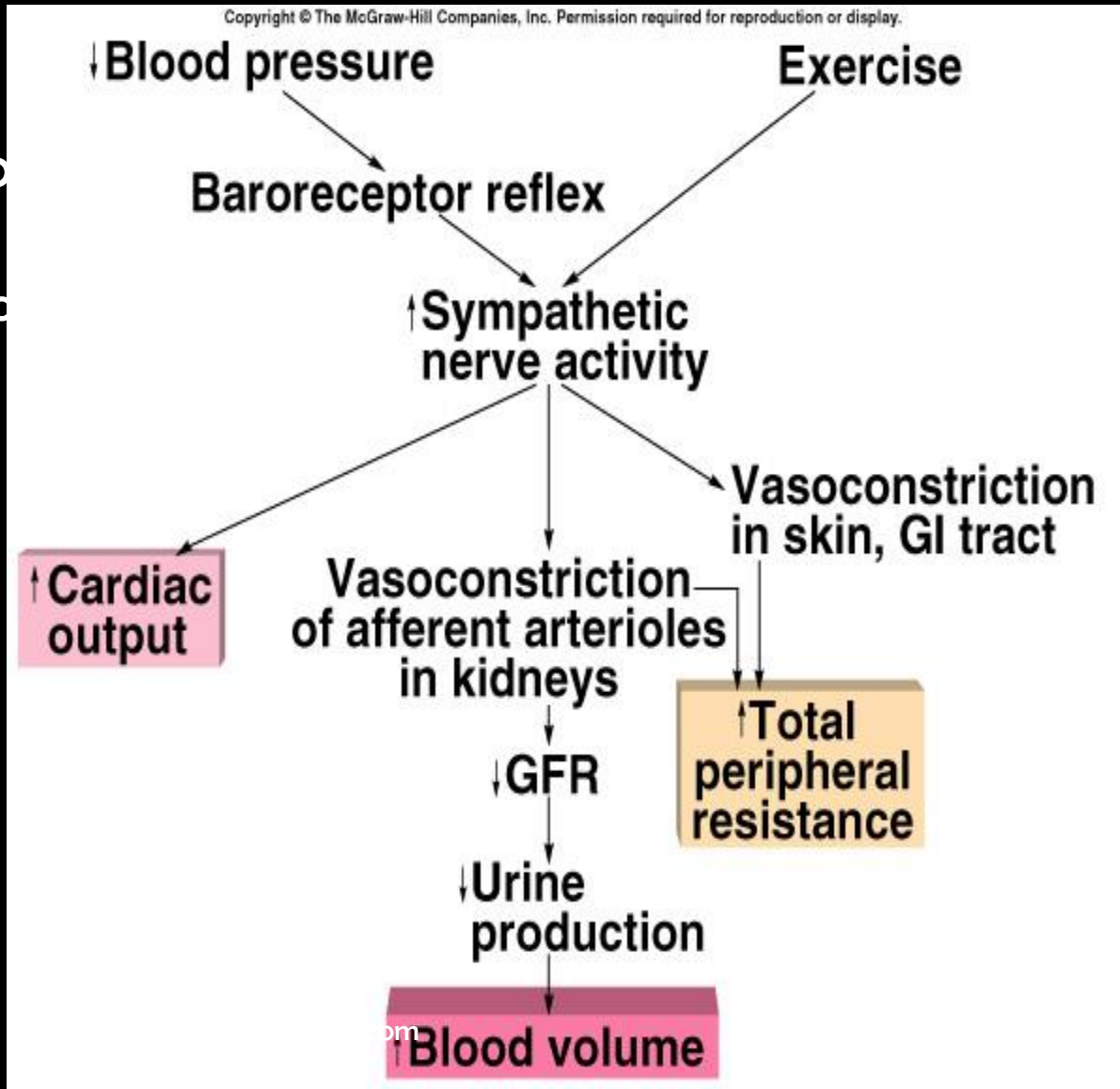
Sympathetic Regulation of GFR

- Stimulates vasoconstrictio of afferent arterioles.
  - Preserves blood volume to muscles and heart.
- Cardiovascular shock:
  - Decreases glomerular capillary hydrostatic pressure.
  - Decreases urine output (UO).



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Renal Autoregulation of GFR

- Ability of kidney to maintain a constant GFR under systemic changes.
  - Achieved through effects of locally produced chemicals on the afferent arterioles.
- When MAP drops to 70 mm Hg, afferent arteriole dilates.
- When MAP increases, vasoconstrict afferent arterioles.
- Tubuloglomerular feedback:
  - Increased flow of filtrate sensed by macula densa cells in thick ascending LH.
    - Signals afferent arterioles to constrict.

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Reabsorption of Salt and H_2O

- Return of most of the molecules and H_2O from the urine filtrate back into the peritubular capillaries.
  - About 180 L/day of ultrafiltrate produced; however, only 1–2 L of urine excreted/24 hours.
    - Urine volume varies according to the needs of the body.
- Minimum of 400 ml/day urine necessary to excrete metabolic wastes (obligatory water loss).

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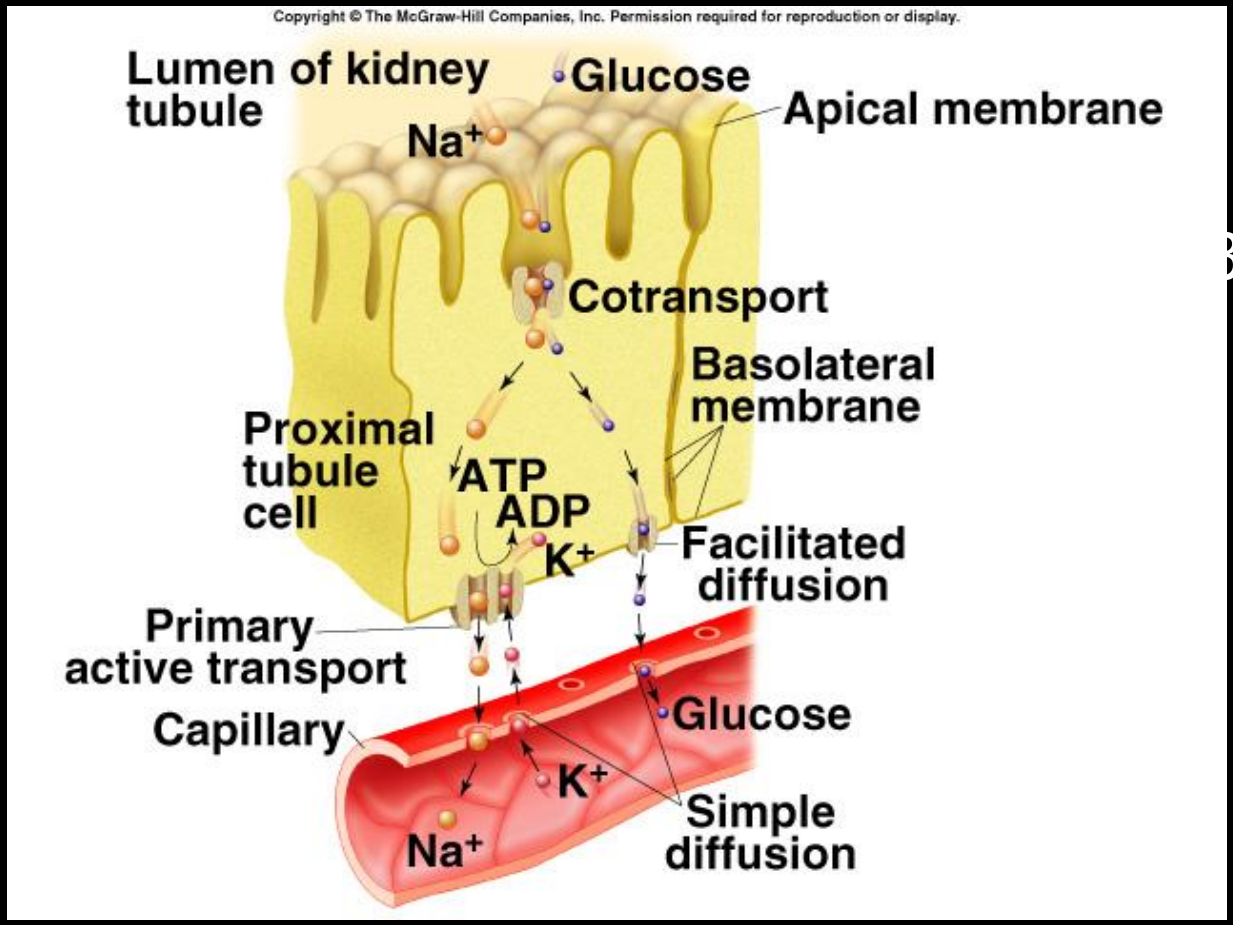
Reabsorption in Proximal Tubule



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PCT

- Total [solute] is = 300 mOsm/L.
- Reabsorption of H_2O by osmosis, cannot occur without active transport:
  - [Na^+] in glomerular ultrafiltrate is 300 mOm/L.
    - PCT epithelial cells have lower [Na^+].
- Due to low permeability of plasma membrane to Na^+.
  - Active transport of Na^+ out of the cell by Na^+/K^+ pumps.
    - Favors [Na^+] gradient:
      - Na^+ diffusion into cell.

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PCT (continued)

- Na^+/K^+ ATPase pump located in basal and lateral sides of cell membrane, creates gradient for diffusion of Na^+ across the apical membrane.
- Na^+/K^+ ATPase pump extrudes Na^+.
  - Creates potential difference across the wall of the tubule, with lumen as –pole.
- Electrical gradient causes Cl^- movement towards higher [Na^+].
  - H_2O follows by osmosis.

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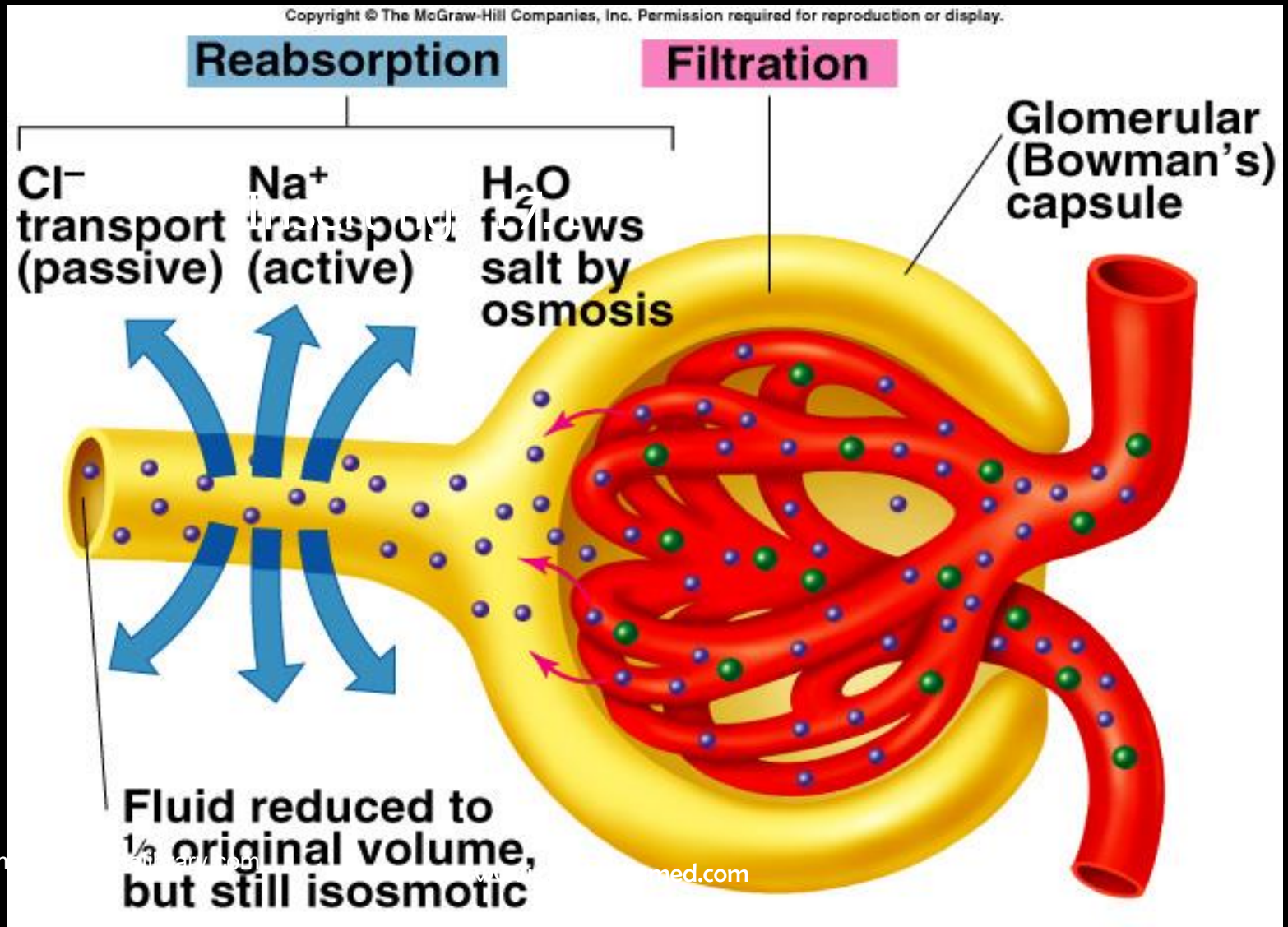
Salt and Water Reabsorption in Proximal Tubule



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Significance of PCT Reabsorption

- 65% Na^+, Cl^-, and H_2O reabsorbed across the PCT into the vascular system.
- 90% K^+ reabsorbed.
- Reabsorption occurs constantly regardless of hydration state.
  - Not subject to hormonal regulation.
- Energy expenditure is 6% of calories consumed at rest.

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Countercurrent Multiplier

- In order for H_2O to be reabsorbed, interstitial fluid must be hypertonic.
- Osmotic pressure of the interstitial tissue fluid is 4 x that of plasma.
  - Results partly from the fact that the tubule bends permitting interaction between the descending and ascending limbs.

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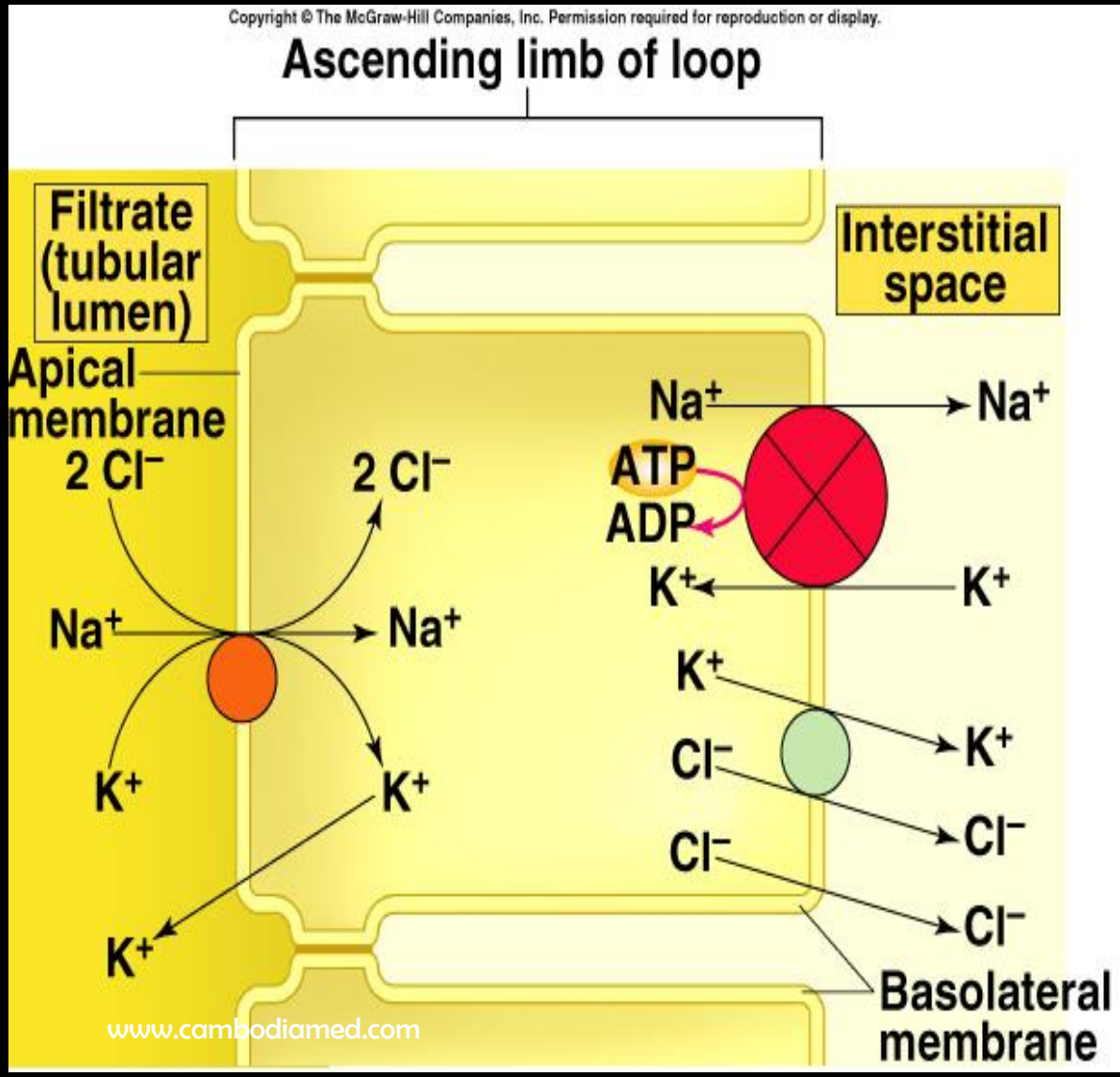
Ascending Limb LH

- NaCl is actively extruded from the ascending limb into surrounding interstitial fluid.
- Na^+ diffuses into tubular cell with the secondary active transport of K^+ and Cl^-.
- Occurs at a ratio of 1 Na^+ and 1 K^+ to 2 Cl^-.



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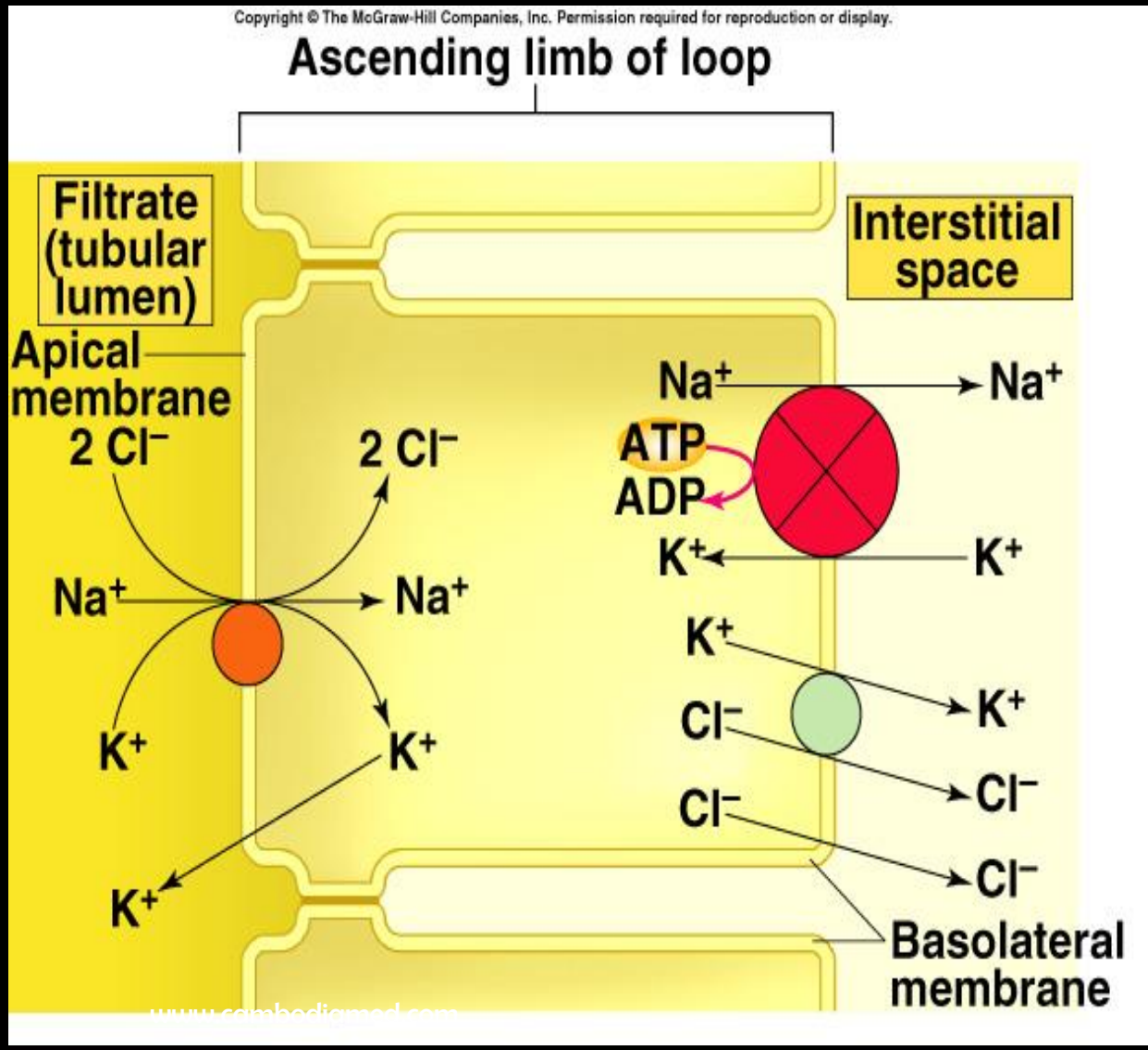
Ascending Limb LH (continued)

- Na^+ actively transported across the basolateral membrane by Na^+/K^+ ATPase pump.
- Cl^- passively follows Na^+ down electrical gradient.
- K^+ passively diffuses back into filtrate.
- Ascending walls are impermeable to H_2O.



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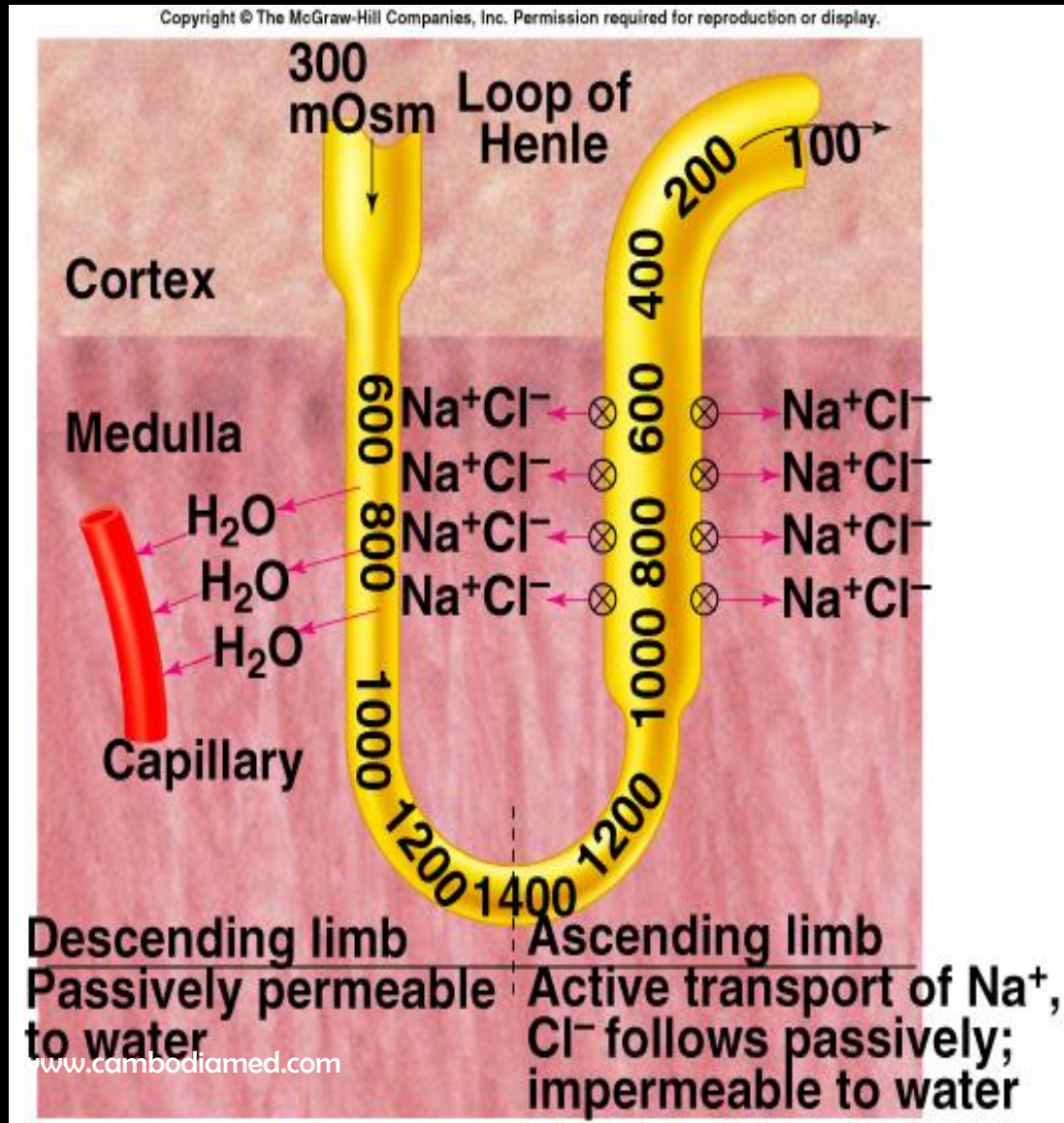
Descending Limb LH

- Deeper regions of medulla reach 1400 mOsm/L.
- Impermeable to passive diffusion of NaCl.
- Permeable to H_2O.
- Hypertonic interstitial fluid causes H_2O movement out of the descending limb via osmosis, and H_2O enters capillaries.
- Fluid volume decreases in tubule, causing higher [Na^+] in the ascending limb.



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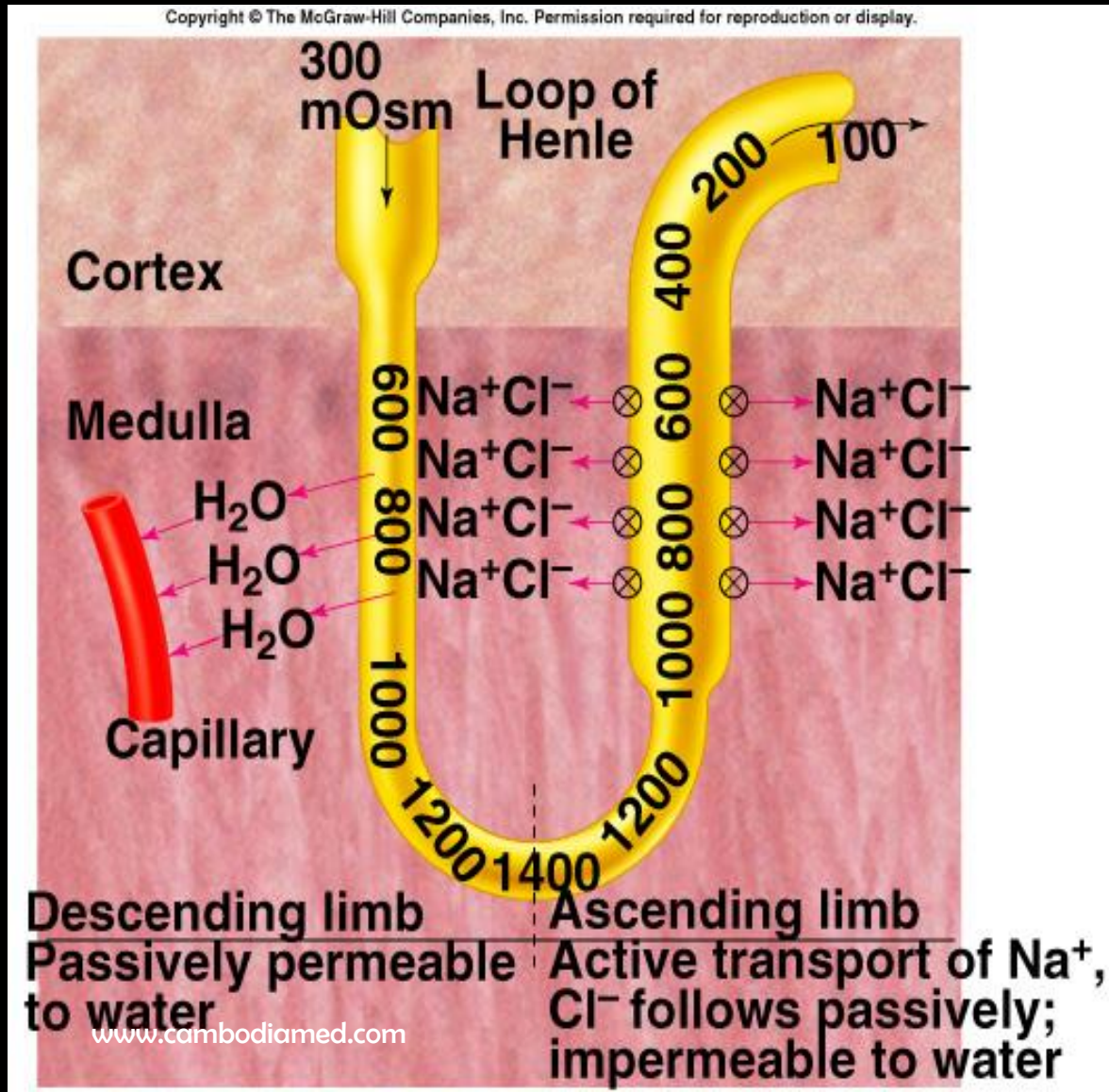
Countercurrent Multiplier System

- Multiplies the [interstitial fluid] and [descending limb fluid].
- Flow in opposite directions in the ascending and descending limbs.
- Close proximity of the 2 limbs:
  - Allows interaction.
- Positive feedback.



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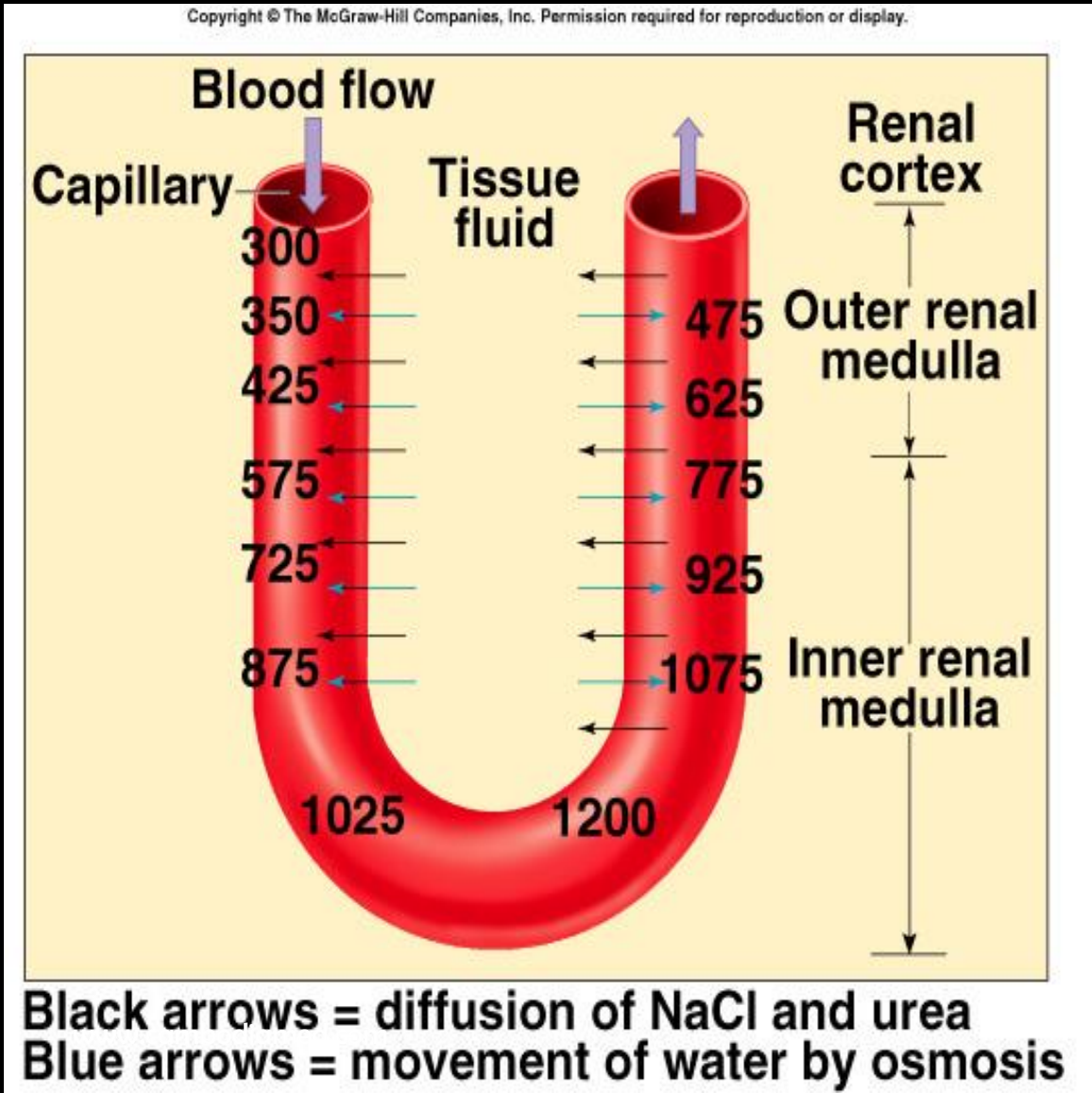
Vasa Recta

- Countercurrent exchange.
- Recycles NaCl in medulla.
- Transports H_2O from interstitial fluid.
- Descending limb:
  - Urea transporters.
  - Aquaporin proteins (H_2O channels).
- Ascending limb:
  - Fenestrated capillaries.



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Vasa Recta (continued)

- Vasa recta maintains hypertonicity by countercurrent exchange.
- NaCl and urea diffuse into descending limb and diffuse back into medullary tissue fluid.
- At each level of the medulla, [solute] is higher in the ascending limb than in the interstitial fluid; and higher in the interstitial fluid than in descending vessels.
- Walls are permeable to H_2O, NaCl and urea.
- Colloid osmotic pressure in vasa recta > interstitial fluid.

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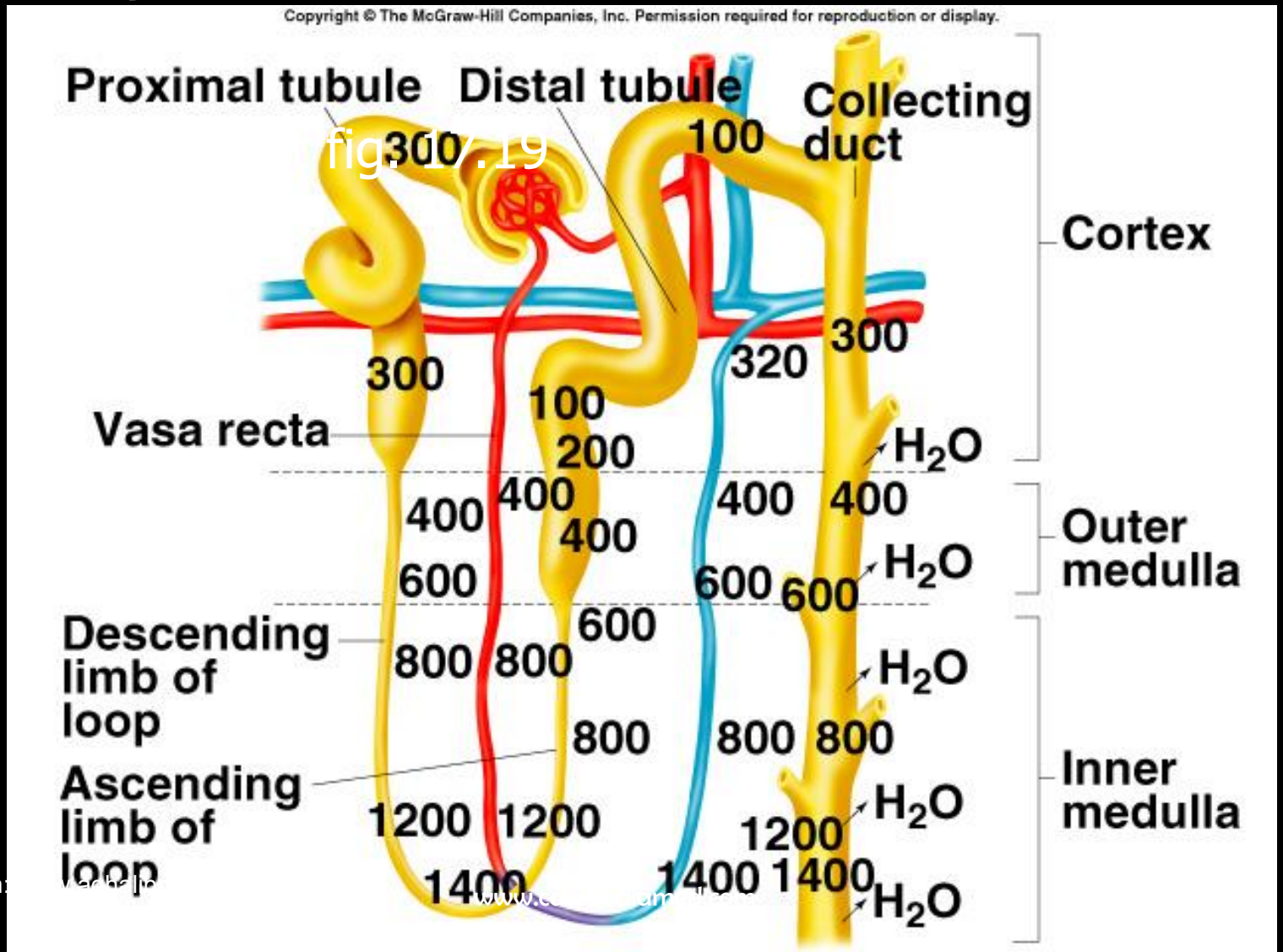
Osmolality of Different Regions of the Kidney



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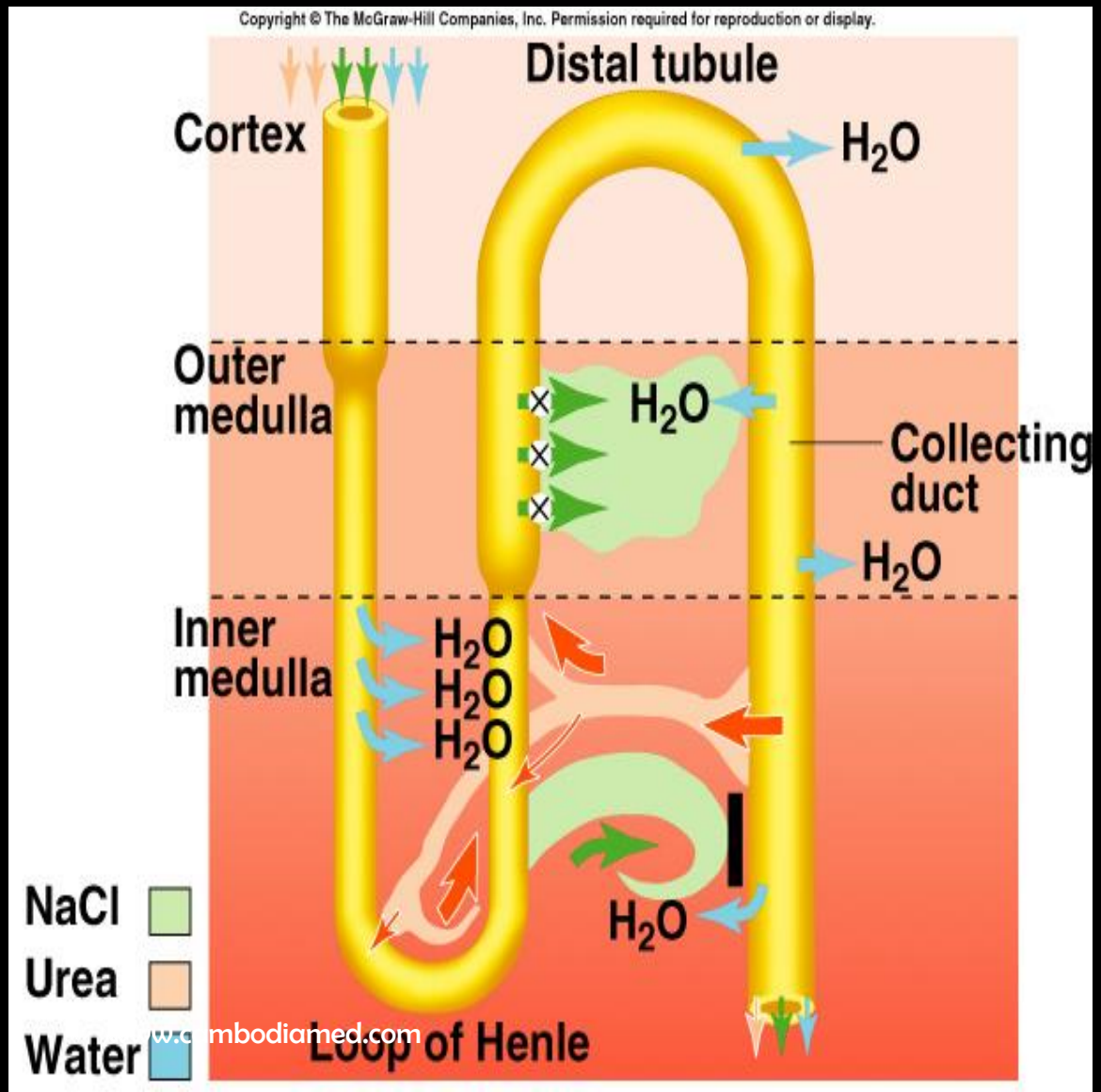
Urea

- Contributes to total osmolality of interstitial fluid.
- Ascending limb LH and terminal CD are permeable to urea.
  - Terminal CD has urea transporters.
- Urea diffuses out CD and into ascending limb LH.
  - Recycle urea.



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Collecting Duct

- Medullary area impermeable to high [NaCl] that surrounds it.
  - The walls of the CD are permeable to H_2O.
- H_2O is drawn out of the CD by osmosis.
  - Rate of osmotic movement is determined by the # of aquaporins in the cell membrane.
- Permeable to H_2O depends upon the presence of ADH.
  - When ADH binds to its membrane receptors on CD, it acts via cAMP.
    - Stimulates fusion of vesicles with plasma membrane.
      - Incorporates water channels into plasma membrane.

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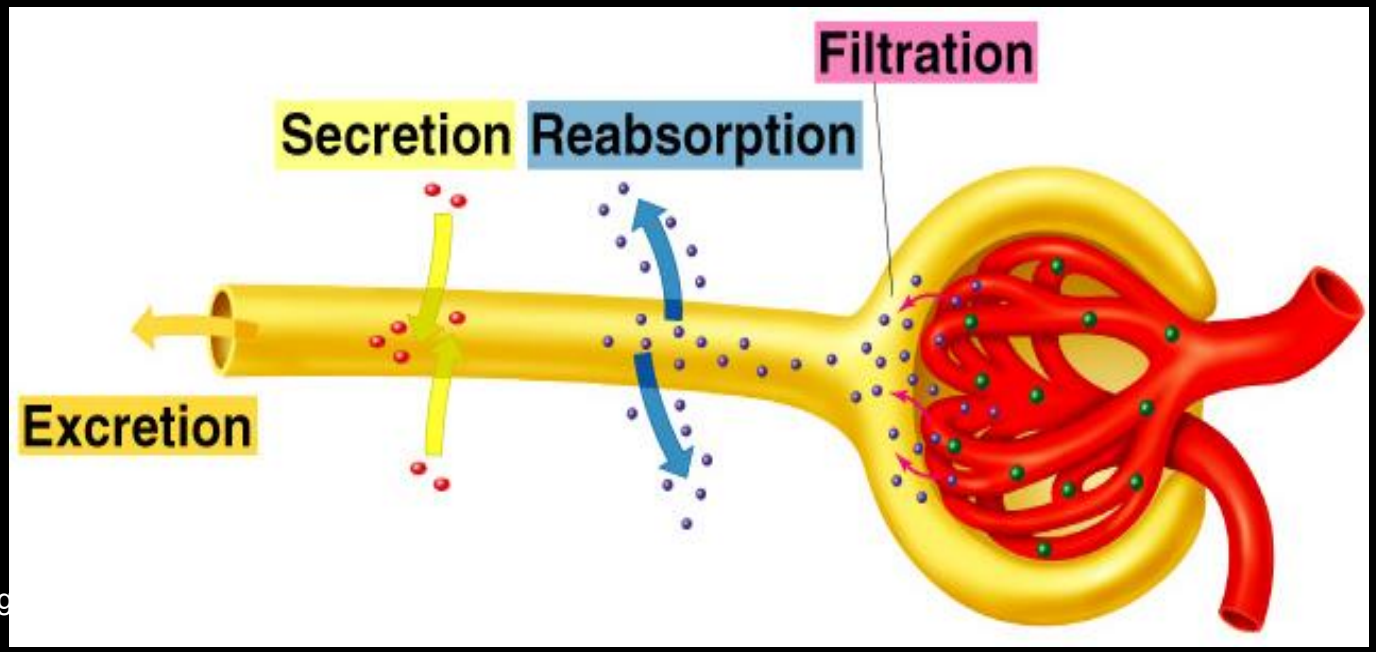
Secretion

- Secretion of substances from the peritubular capillaries into interstitial fluid.
  - Then transported into lumen of tubule, and into the urine.
- Allows the kidneys to rapidly eliminate certain potential toxins.



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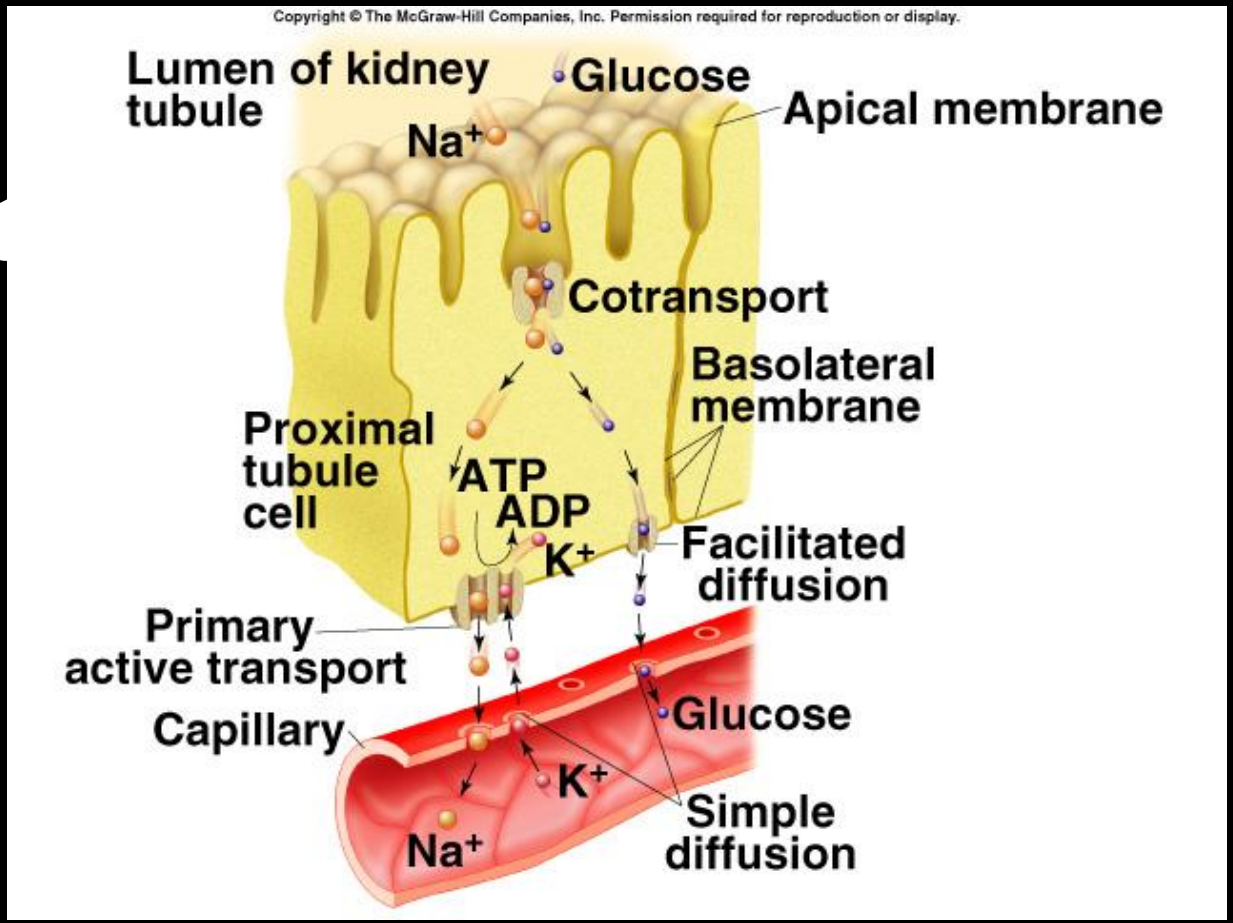
Proximal Tubule

Secret



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Transport Process Affecting Renal Clearance

- Ability of the kidneys to remove molecules from plasma and excrete those molecules in the urine.
- If a substance is not reabsorbed or secreted, then the amount excreted = amount filtered.

Quantity excreted = V x U

- Quantity excreted = mg/min.
- V = rate of urine formation.
- U = inulin concentration in urine.

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Measurement of GFR

- If a substance is neither reabsorbed nor secreted by tubule:
  - The amount excreted in urine/min. will be equal to the amount filtered out of the glomeruli/min.
- Rate at which a substance is filtered by the glomeruli can be calculated:

$$\text{Quantity filtered} = \text{GFR} \times P$$

  - P = inulin concentration in plasma.
- Amount filtered = amount excreted

$$\text{GFR} = \frac{V \times U}{P}$$

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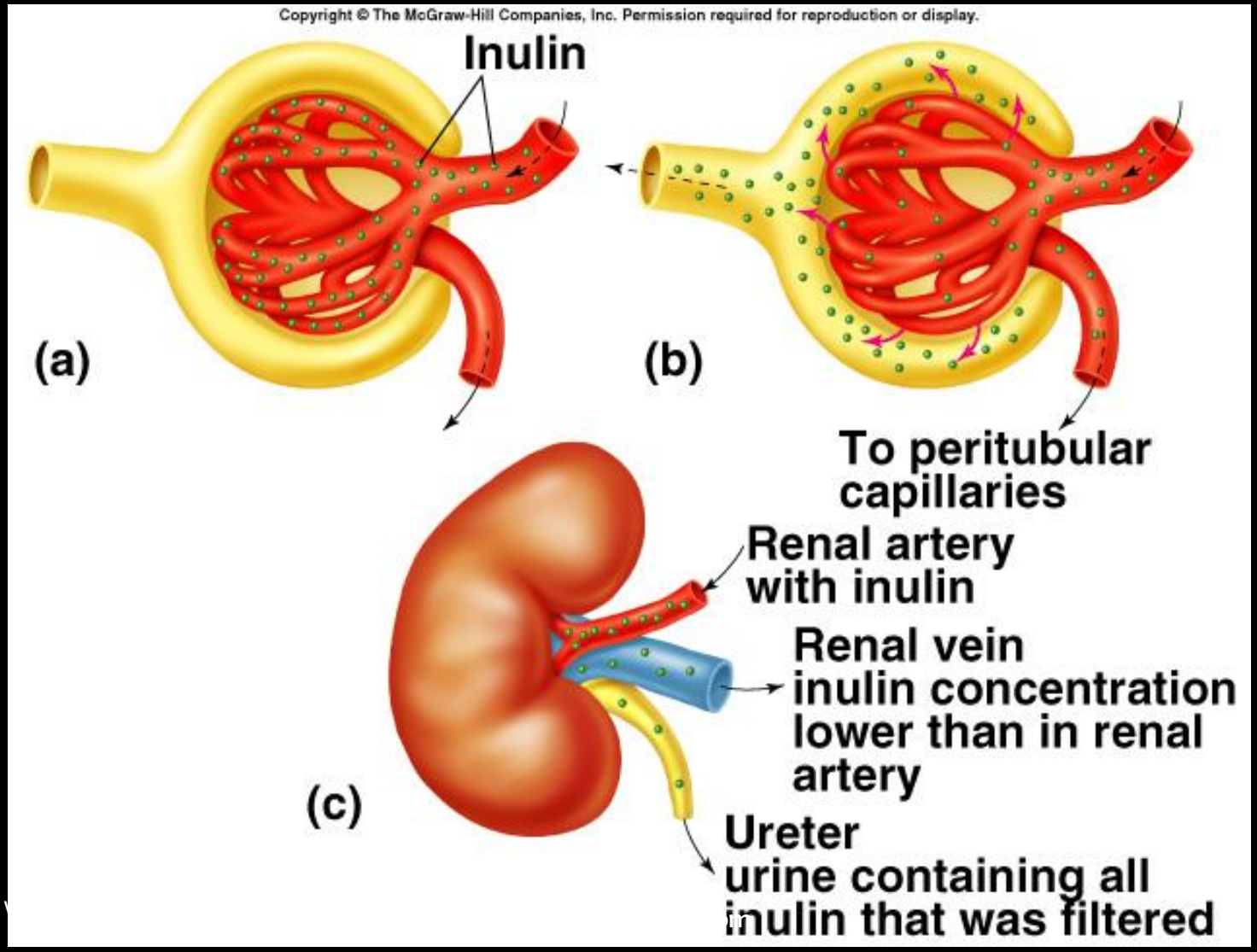
Renal Clearance of Inulin



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Renal Plasma Clearance

- Volume of plasma from which a substance is completely removed in 1 min. by excretion in the urine.
- Substance is filtered, but not reabsorbed:
  - All filtered will be excreted.
- Substance filtered, but also secreted and excreted will be:
  - > GFR (GFR = 120 ml/ min.).

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Renal Plasma Clearance

Renal plasma clearance = $\frac{V \times U}{P}$

- V = urine volume per min.
- U = concentration of substance in urine
- P = concentration of substance in plasma

- Compare renal "handling" of various substances in terms of reabsorption or secretion.

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Clearance of Urea

- Urea is secreted into blood and filtered into glomerular capsule.
- Urea clearance is 75 ml/min., compared to clearance of inulin (120 ml/min.).
  - 40-60% of filtered urea is always reabsorbed.
- Passive process because of the presence of carriers for facilitative diffusion of urea.

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Measurement of Renal Blood Flow

- Not all blood delivered to glomeruli is filtered in the glomerular capsules.
  - Most of glomerular blood passes to the efferent arterioles.
  - 20% renal plasma flow filtered.
    - Substances are returned back to blood.
- Substances in unfiltered blood must be secreted into tubules to be cleared by active transport (PAH).
  - PAH can be used to measure renal plasma flow.

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Measurement of Renal Blood Flow (continued)

- Filtration and secretion clear only the molecules dissolved in plasma.
  - PAH clearance actually measures renal plasma flow.
- To convert to total renal blood flow, the amount of blood occupied by erythrocytes must be taken into account.
  - Averages 625 ml/min.

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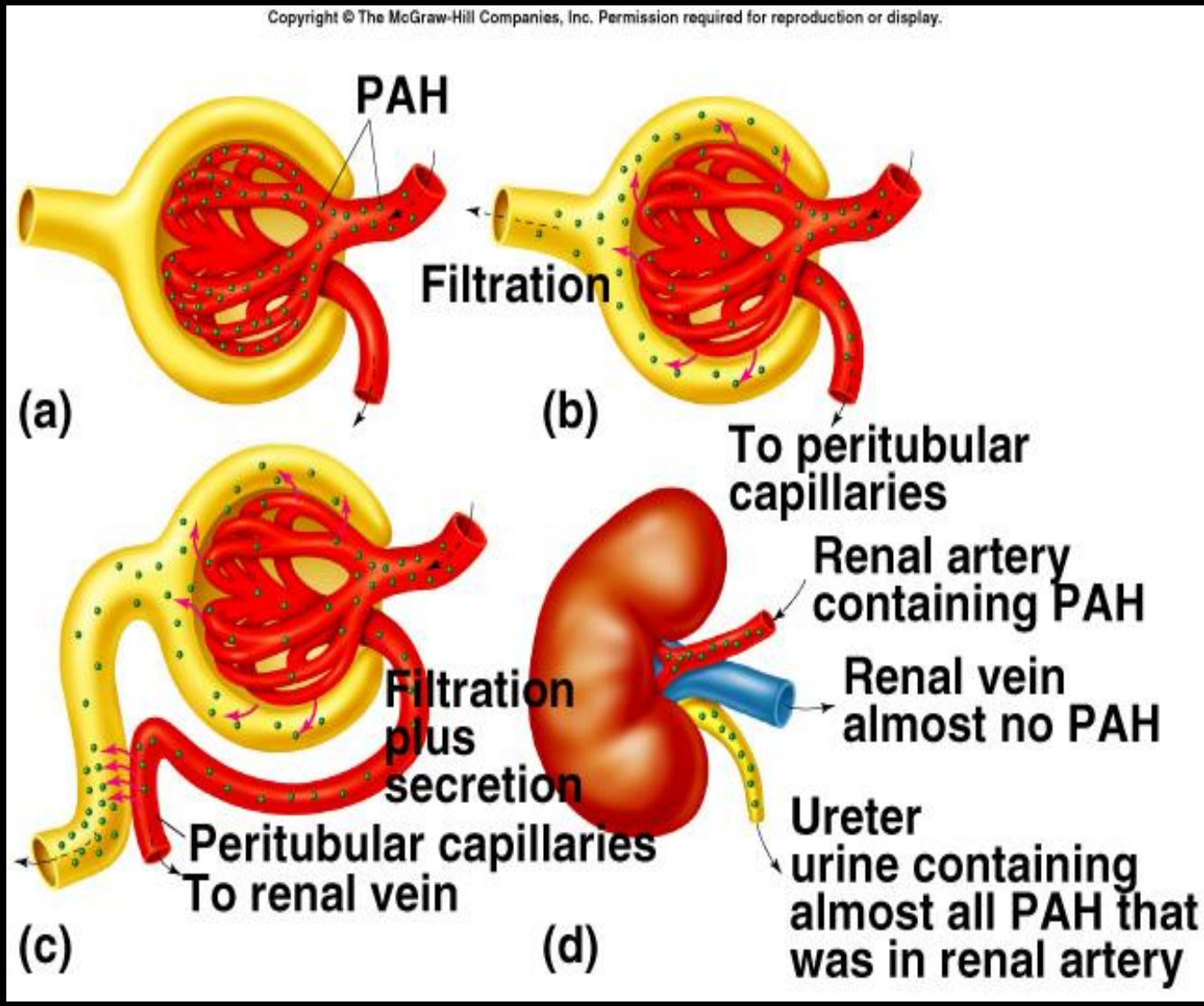
Total Renal Blood Flow

- 45% blood is RBCs
- 55% plasma
- Total renal blood flow = PAH clearance

  0.55



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Glucose and Amino Acid Reabsorption

- Filtered glucose and amino acids are normally reabsorbed by the nephrons.
  - In PCT occurs by secondary active transport with membrane carriers.
    - Carrier mediated transport displays:
      - Saturation.
      - T_m.
        - [Transported molecules] needed to saturate carriers and achieve maximum transport rate.
- Renal transport threshold:
  - Minimum plasma [substance] that results in excretion of that substance in the urine.
    - Renal plasma threshold for glucose = 180-200 mg/dl.

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Electrolyte Balance

- Kidneys regulate Na^+, K^+, H^+, Cl^-, HCO_3^-, and PO_4^{-3}.
- Control of plasma Na^+ is important in regulation of blood volume and pressure.
- Control of plasma of K^+ important in proper function of cardiac and skeletal muscles.
  - Match ingestion with urinary excretion.

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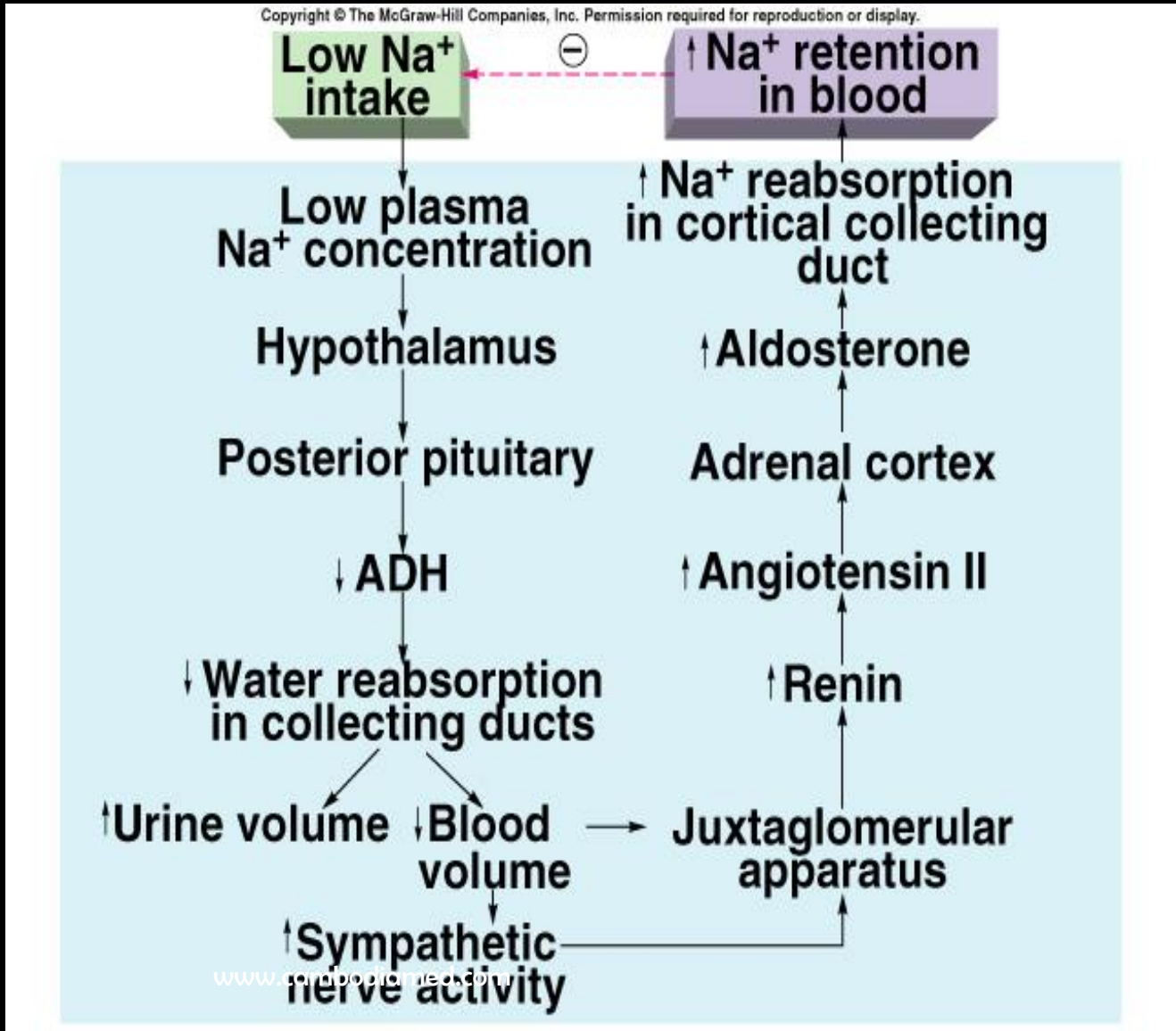
Na^+ Reabsorption

- 90% filtered Na^+ reabsorbed in PCT.
- In the absence of aldosterone, 80% of the remaining Na^+ is reabsorbed in DCT.
- Final [Na^+] controlled in CD by aldosterone.
- When aldosterone is secreted in maximal amounts, all Na^+ in DCT is reabsorbed.



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K^+ Secretion

- 90% filtered K^+ is reabsorbed in early part of the nephron.
- Secretion of K^+ occurs in CD.
  - Amount of K^+ secreted depends upon:
    - Amount of Na^+ delivered to the region.
    - Amount of aldosterone secreted.
  - As Na^+ is reabsorbed, lumen of tubule becomes –charged.
    - Potential difference drives secretion of K^+ into tubule.
      - Transport carriers for Na^+ separate from transporters for K^+.

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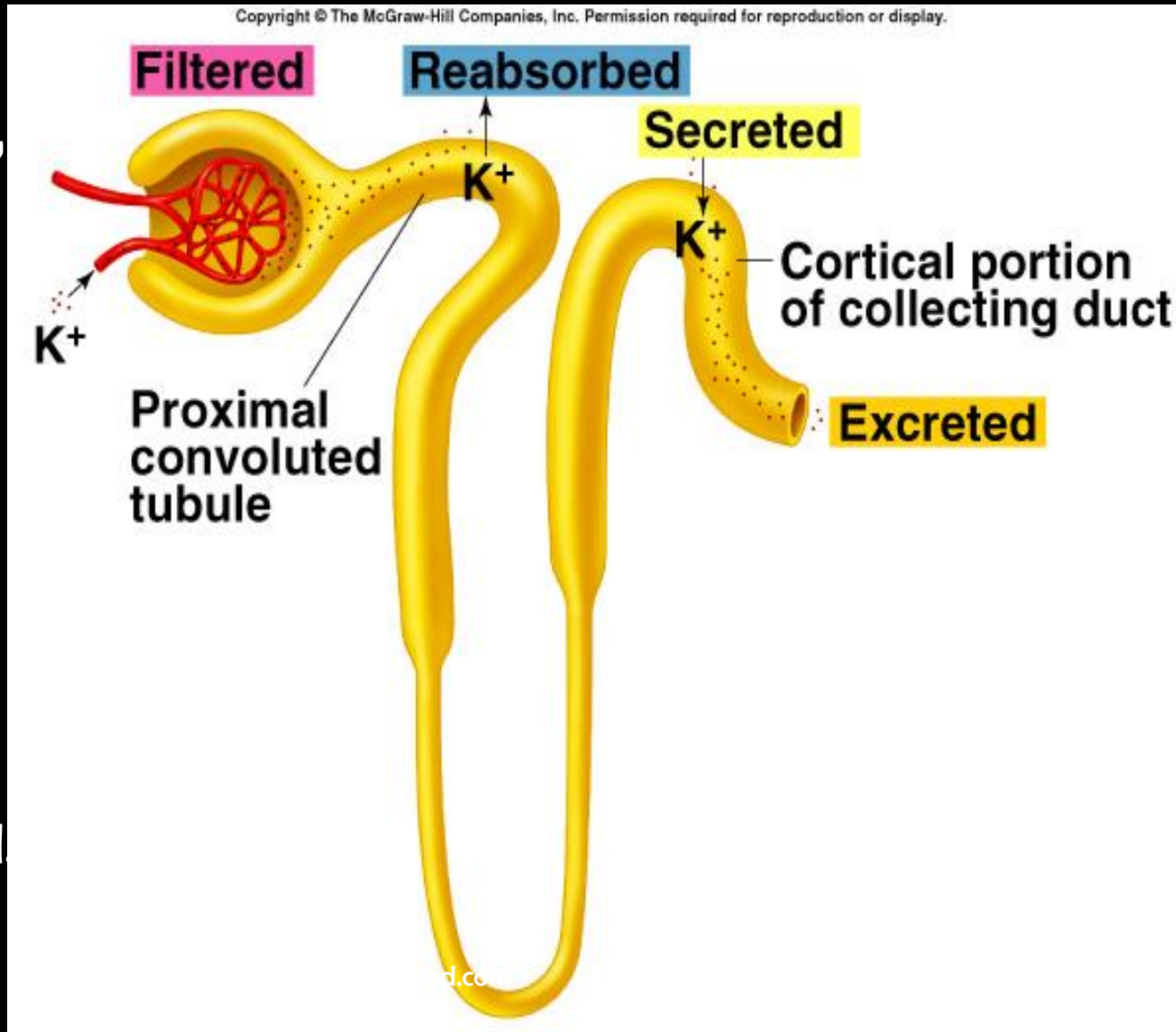
K^+ Secretion (continued)

- Final $[K^+]$ controlled in CD by aldosterone.
  - When aldosterone is absent, no K^+ is excreted in the urine.
- High $[K^+]$ or low $[Na^+]$ stimulates the secretion of aldosterone.
- Only means by which K^+ is secreted.



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Juxtaglomerular Apparatus

- Region in each nephron where the afferent arteriole comes in contact with the thick ascending limb LH.
- Granular cells within afferent arteriole secrete renin:
    - Converts angiotensinogen to angiotensin I.
    - Initiates the renin-angiotensin-aldosterone system.
    - Negative feedback.
- Macula densa:
    - Region where ascending limb is in contact with afferent arteriole.
    - Inhibits renin secretion when blood [Na^+] in blood increases.

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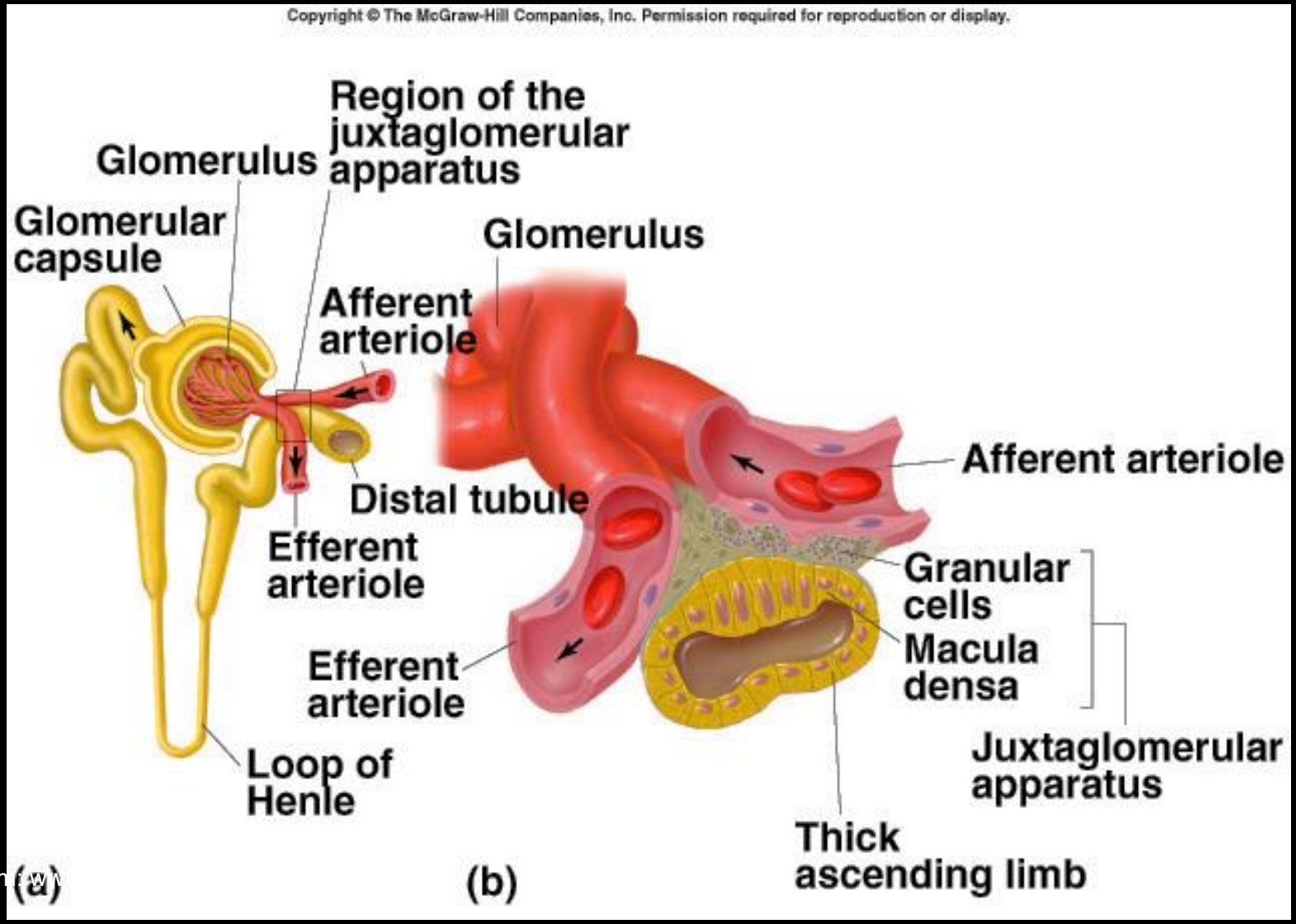
Juxtaglomerular Apparatus (continued)



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ANP

- Produced by atria due to stretching of walls.
- Antagonist to aldosterone.
- Increases Na^+ and H_2O excretion.
- Acts as an endogenous diuretic.

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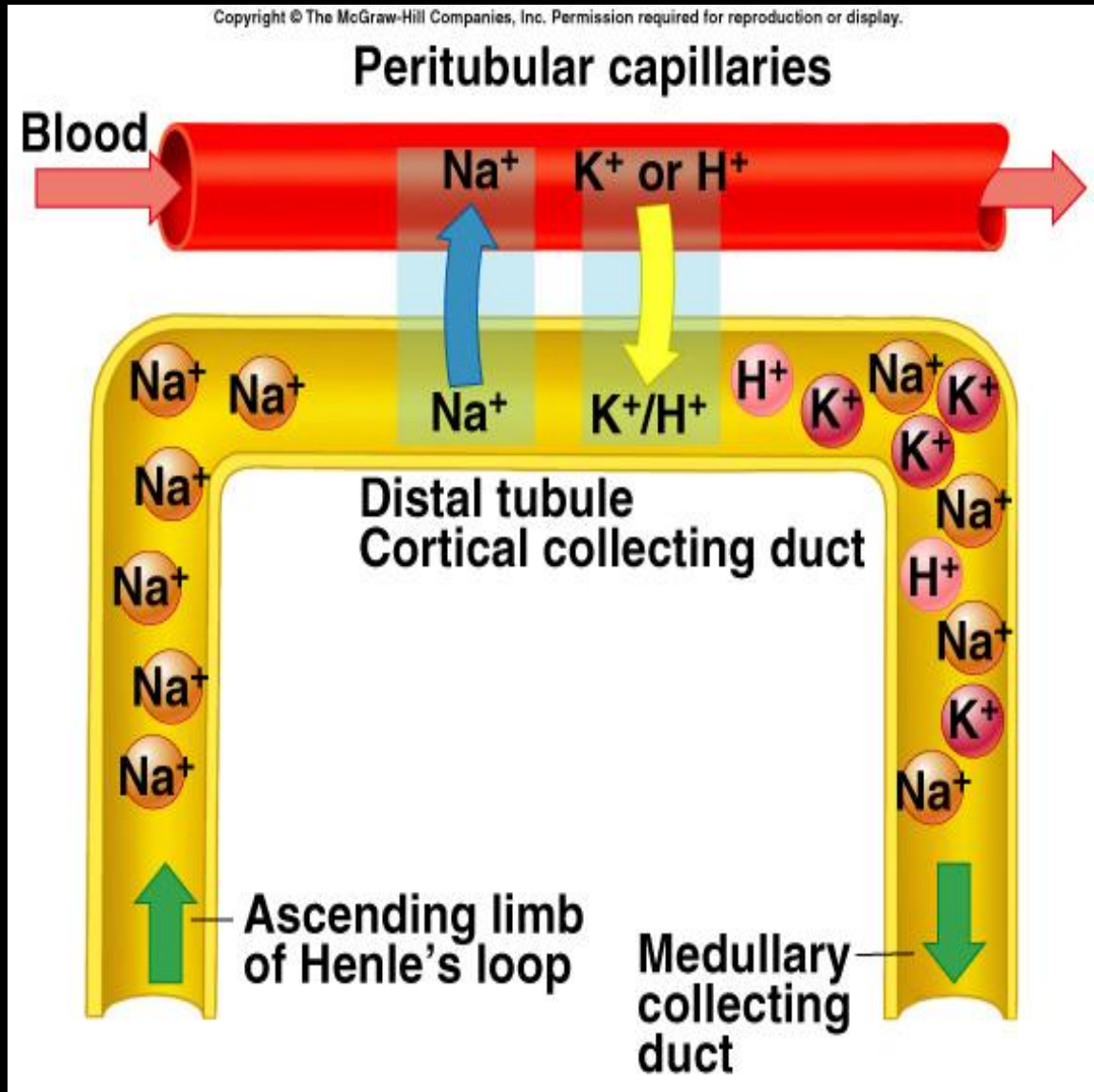
Na^+, K^+, and H^+ Relationship

- Na^+ reabsorption in CD creates electrical gradient for K^+ secretion.
- Plasma $[K^+]$ indirectly affects $[H^+]$.
- When extracellular $[H^+]$ increases, H^+ moves into the cell, causing K^+ to diffuse into the ECF.
- In severe acidosis, H^+ is secreted at the expense of K^+.



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Renal Acid-Base Regulation

- Kidneys help regulate blood pH by excreting H^+ and reabsorbing HCO_3^-.
- Most of the H^+ secretion occurs across the walls of the PCT in exchange for Na^+.
  - Antiport mechanism.
    - Moves Na^+ and H^+ in opposite directions.
- Normal urine normally is slightly acidic because the kidneys reabsorb almost all HCO_3^- and excrete H^+.
  - Returns blood pH back to normal range.

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Reabsorption of HCO_3^-

- Apical membranes of tubule cells are impermeable to HCO_3^-.
  - Reabsorption is indirect.
- When urine is acidic, HCO_3^- combines with H^+ to form $H_2CO_3^-$, which is catalyzed by ca located in the apical cell membrane of PCT.
  - As [CO_2] increases in the filtrate, CO_2 diffuses into tubule cell and forms H_2CO_3.
  - H_2CO_3 dissociates to HCO_3^- and H^+.
- HCO_3^- generated within tubule cell diffuses into peritubular capillary.

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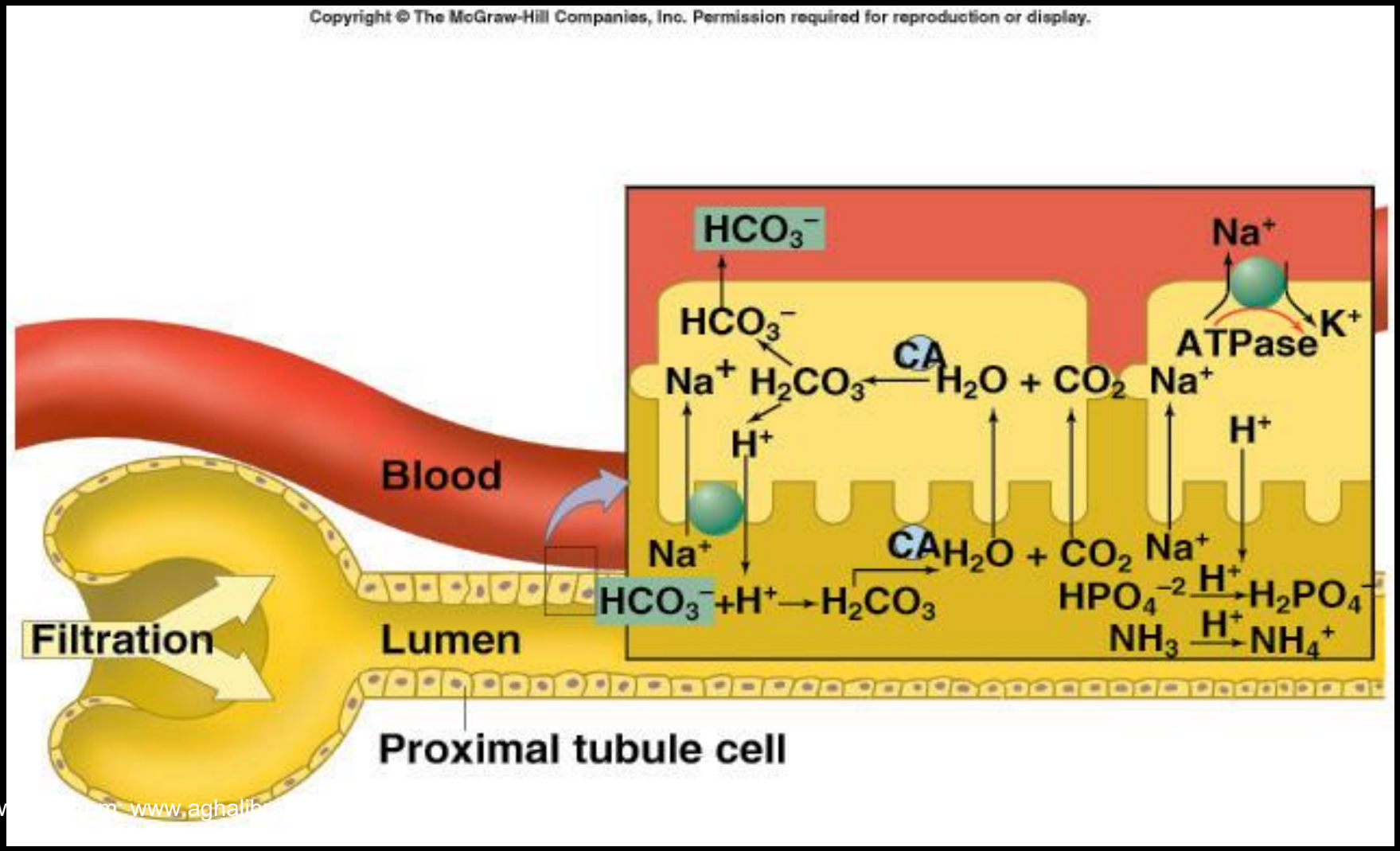
Acidification of Urine



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Urinary Buffers

- Nephron cannot produce a urine pH < 4.5.
- In order to excrete more H^+, the acid must be buffered.
- H^+ secreted into the urine tubule and combines with HPO_4^{-2} or NH_3.
- $HPO_4^{-2} + H^+ \rightarrow H_2PO_4^-$
- $NH_3 + H^+ \rightarrow NH_4^+$

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Diuretics

- Increase urine volume excreted.
  - Increase the proportion of glomerular filtrate that is excreted as urine.
- Loop diuretics:
  - Inhibit NaCl transport out of the ascending limb of the LH.
- Thiazide diuretics:
  - Inhibit NaCl reabsorption in the 1st segment of the DCT.
- Ca inhibitors:
  - Prevent H_2O reabsorption in PCT when HCO_s^- is reabsorbed.
- Osmotic diuretics:
  - Increase osmotic pressure of filtrate.

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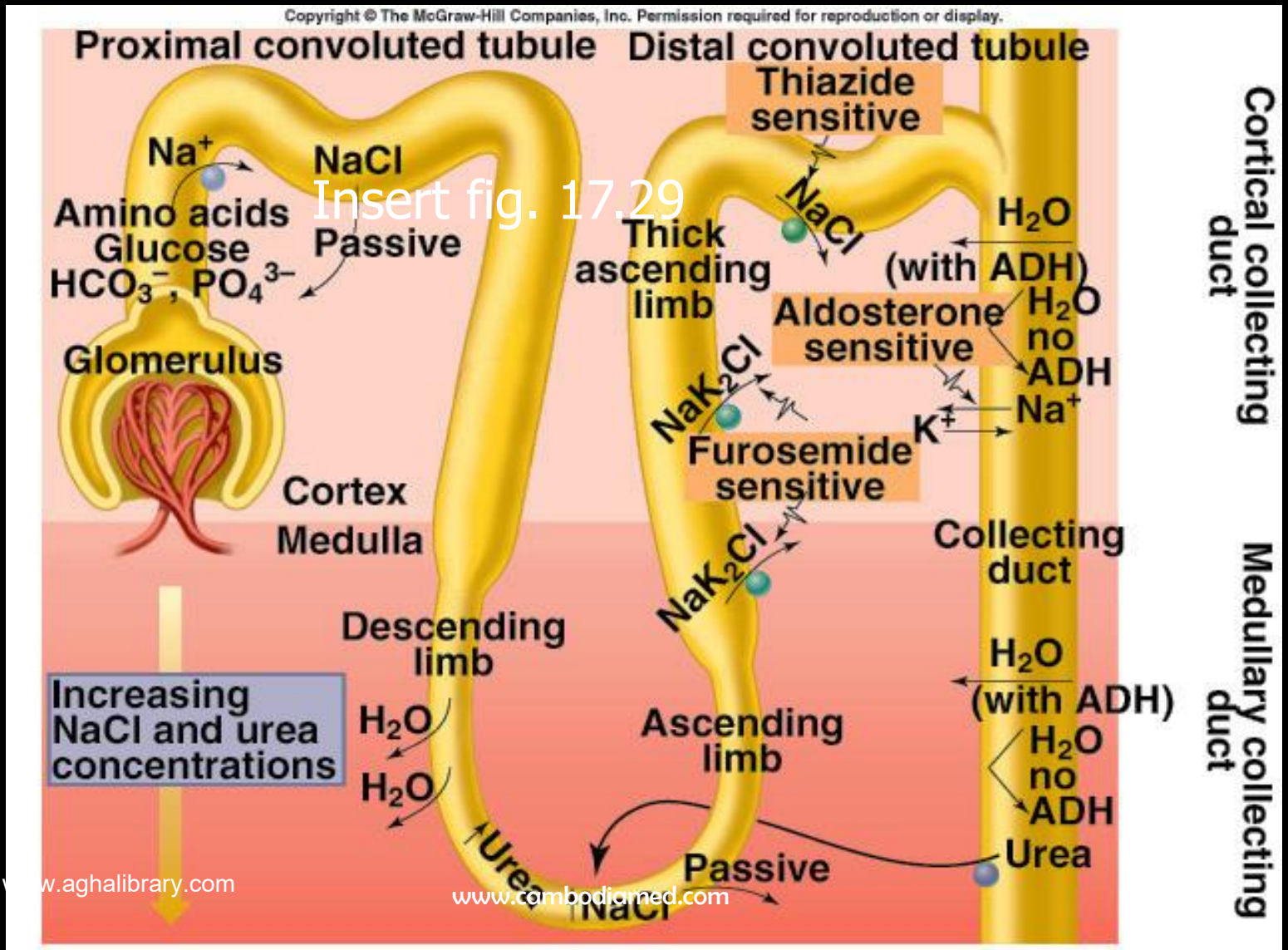
Clinical Diuretics Sites of Action



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Kidney Diseases

- Acute renal failure:
  - Ability of kidneys to excrete wastes and regulate homeostasis of blood volume, pH, and electrolytes impaired.
    - Rise in blood [creatinine].
    - Decrease in renal plasma clearance of creatinine.
- Glomerulonephritis:
  - Inflammation of the glomeruli.
  - Autoimmune disease by which antibodies have been raised against the glomerulus basement membrane.
    - Leakage of protein into the urine.

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Kidney Diseases (continued)

- Renal insufficiency:
  - Nephrons are destroyed.
  - Clinical manifestations:
    - Salt and H_2O retention.
    - Uremia.
    - Elevated plasma $[H^+]$ and $[K^+]$.
- Dialysis:
  - Separates molecules on the basis of the ability to diffuse through selectively permeable membrane.

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