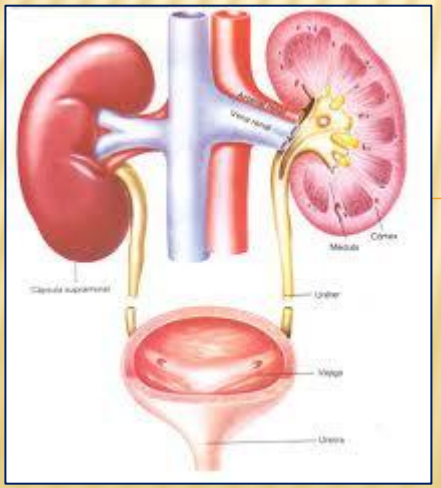
MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DISTANCE LEARNING CENTER

Lecture № 18

URINE FORMATION BY THE KIDNEYS. GLOMERULAR FILTRATION. TUBULAR REABSORPTION AND SECRETION. URINE CONCENTRATION AND DILUTION. MICTURITION



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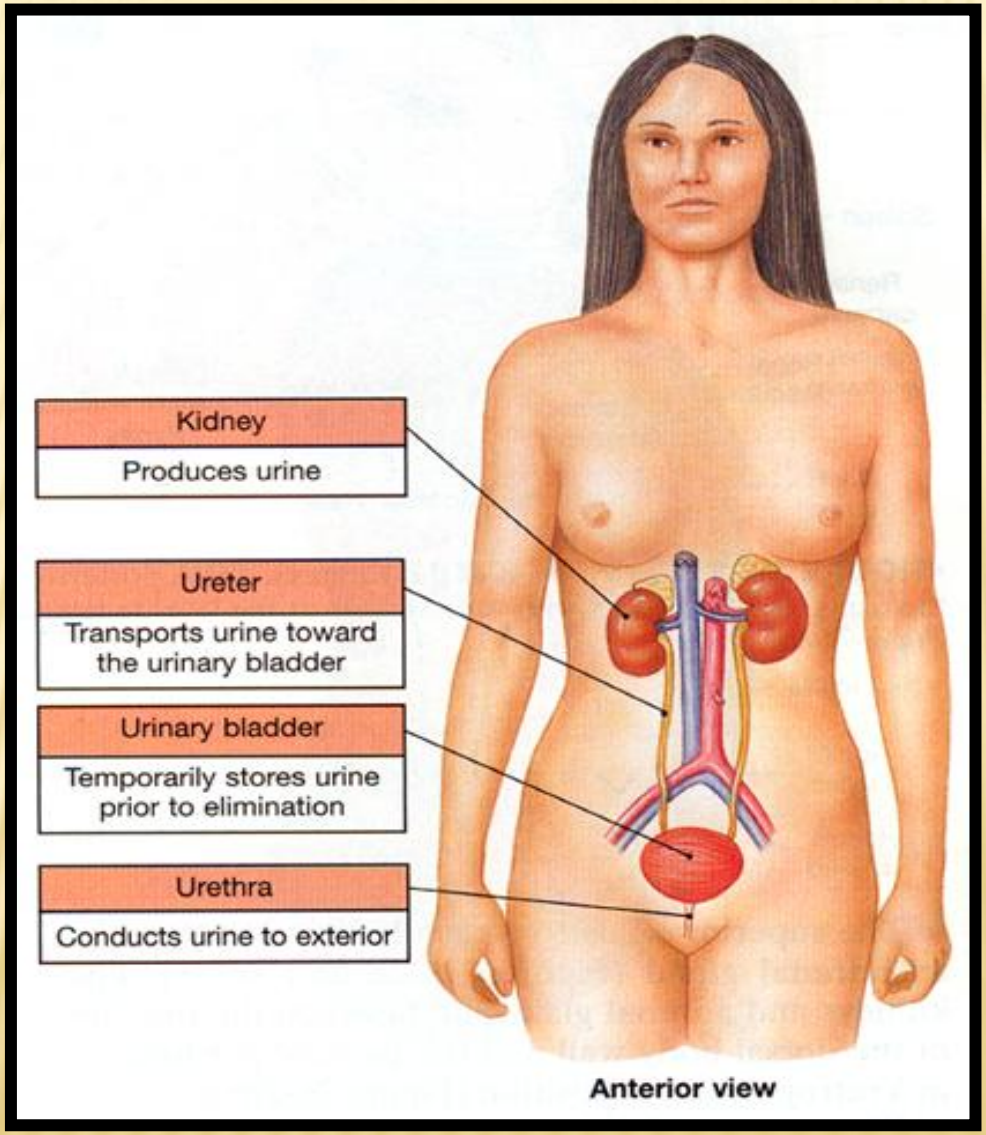
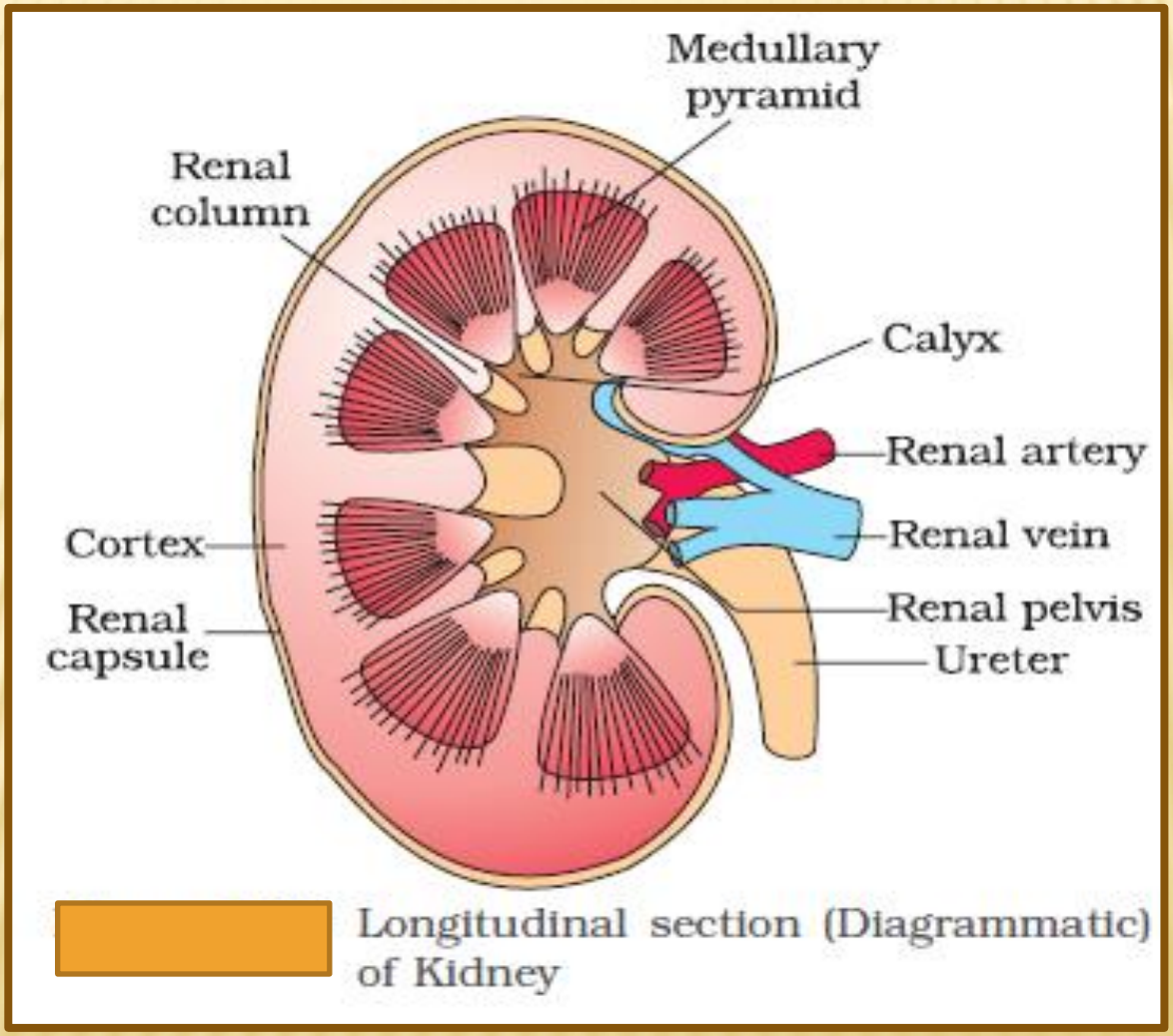
MULTIPLE FUNCTIONS OF THE KIDNEYS IN HOMEOSTASIS

- Excretion of metabolic waste products and foreign chemicals
- Regulation of water and electrolyte balances
- Regulation of body fluid osmolality and electrolyte concentrations
- Regulation of arterial pressure
- Regulation of acid-base balance
- Secretion, metabolism, and excretion of hormones
- Gluconeogenesis

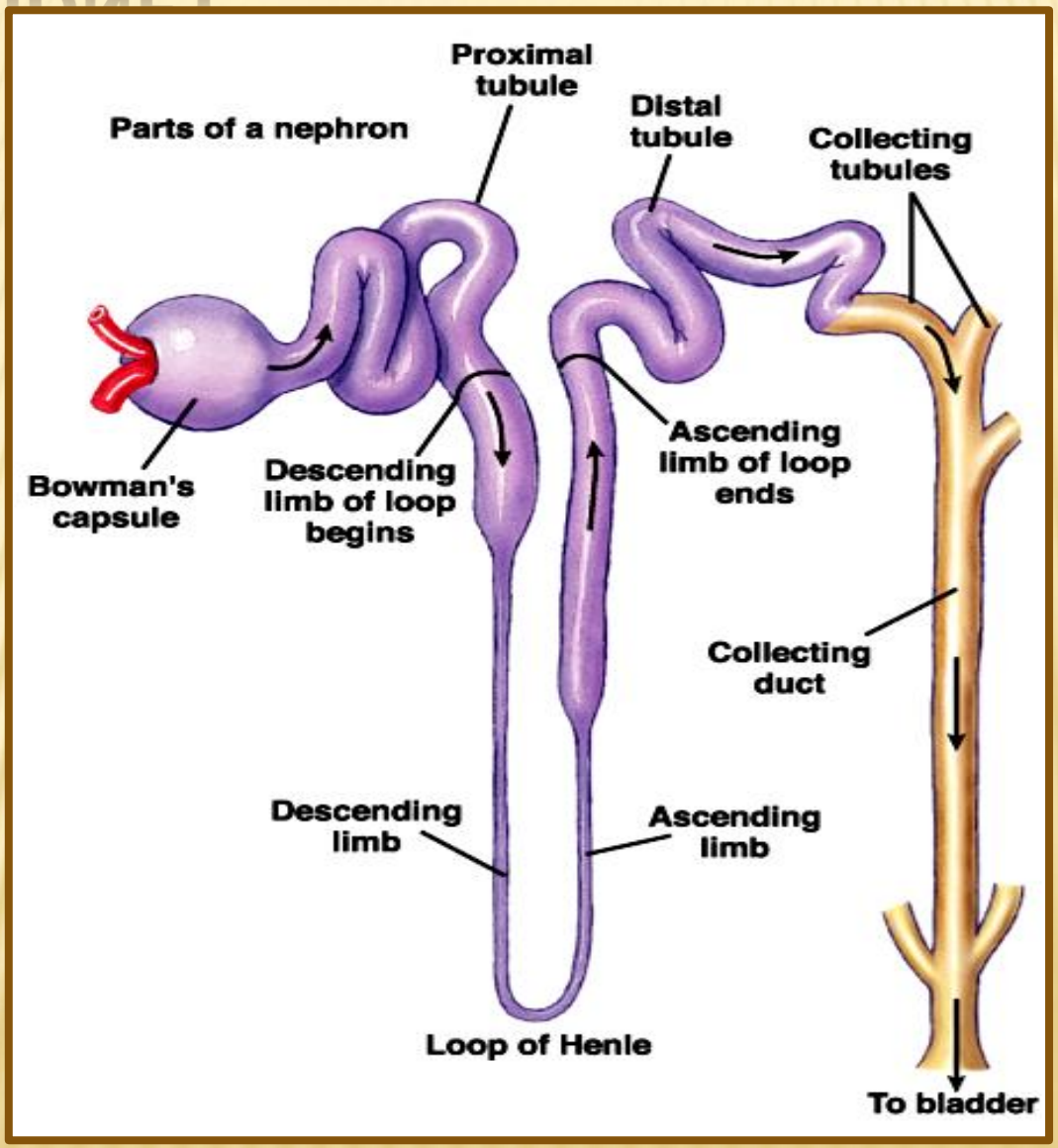
GENERAL ORGANIZATION OF THE KIDNEYS AND URINARY TRACT



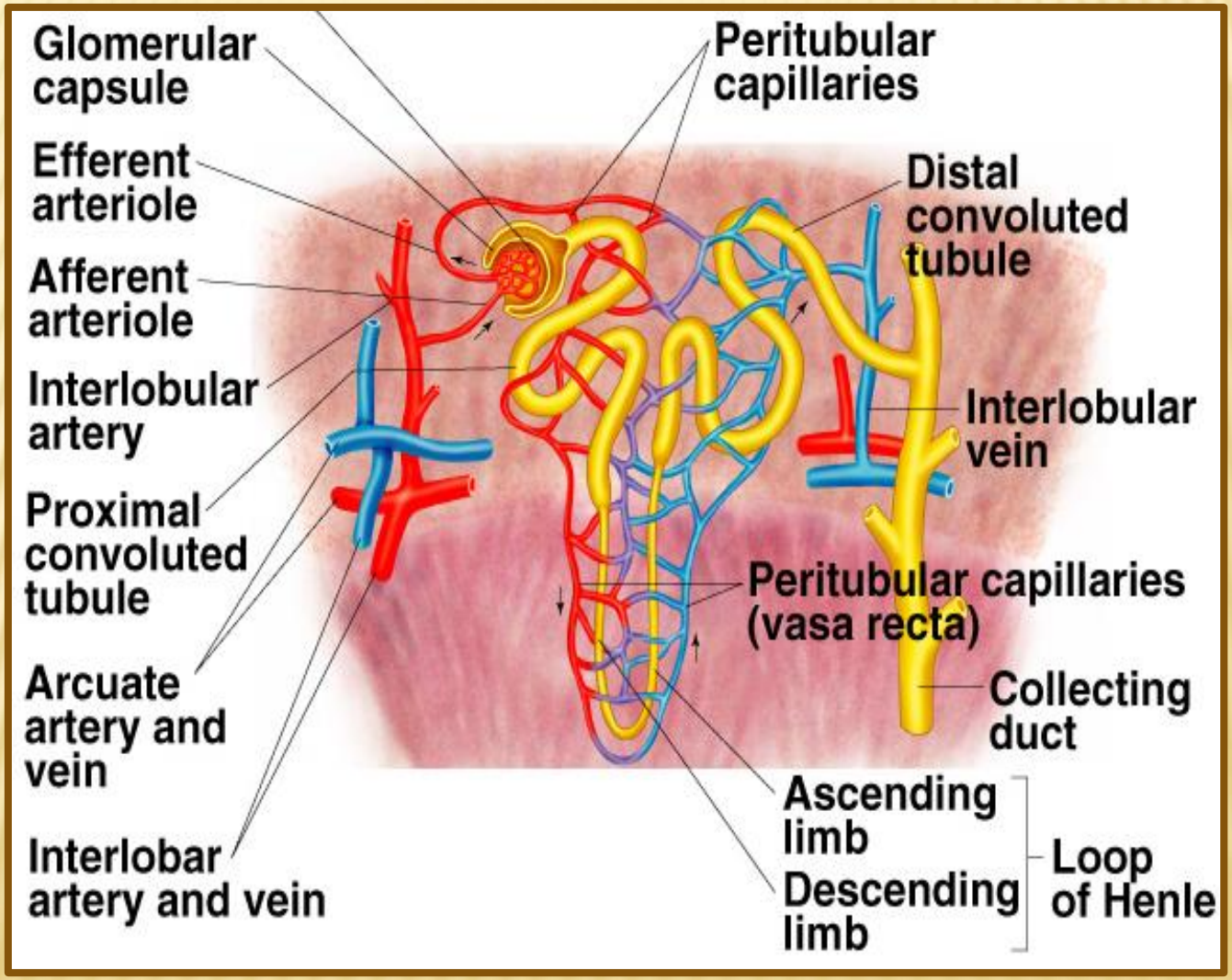
ANATOMY OF THE KIDNEY



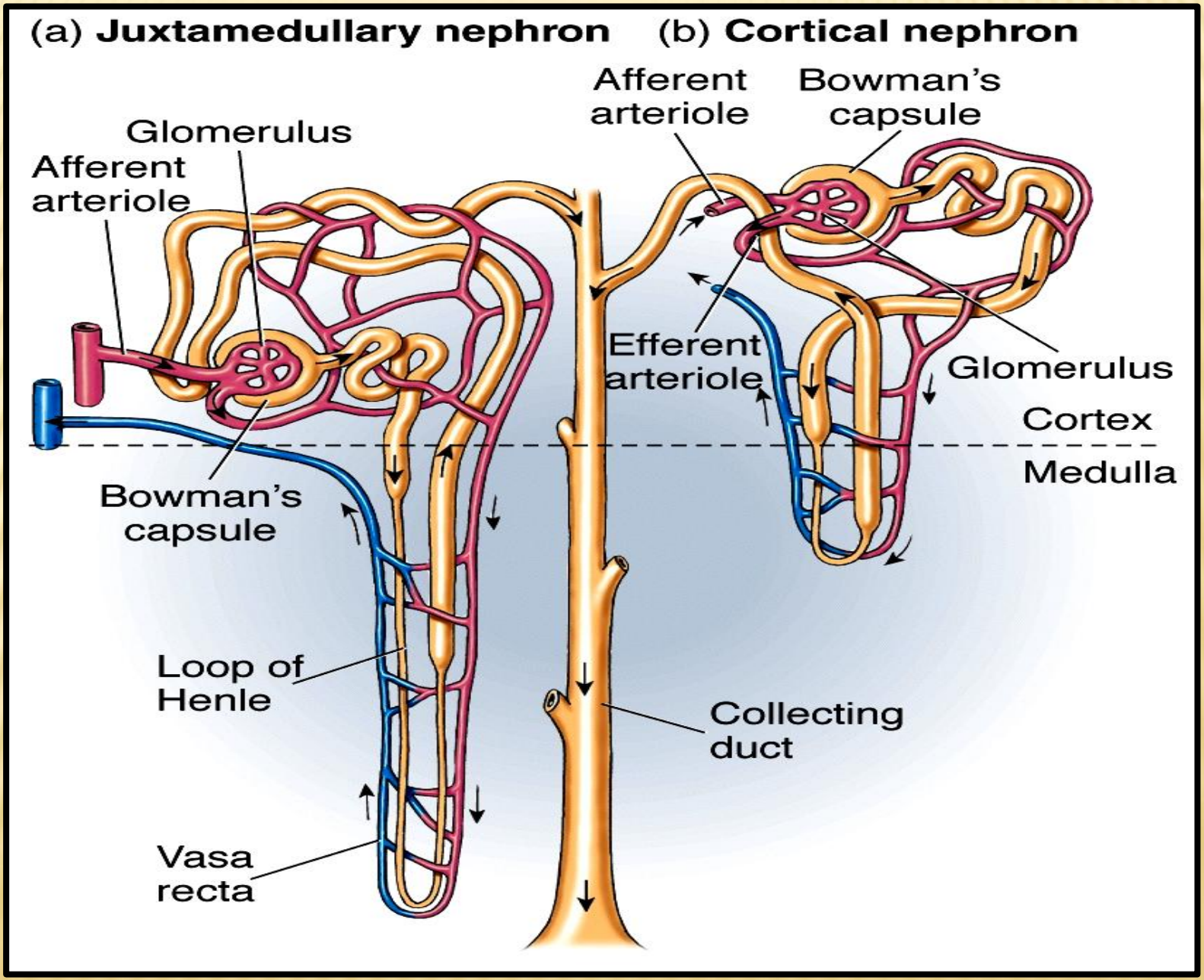
THE NEPHRON IS THE FUNCTIONAL UNIT OF THE KIDNEY



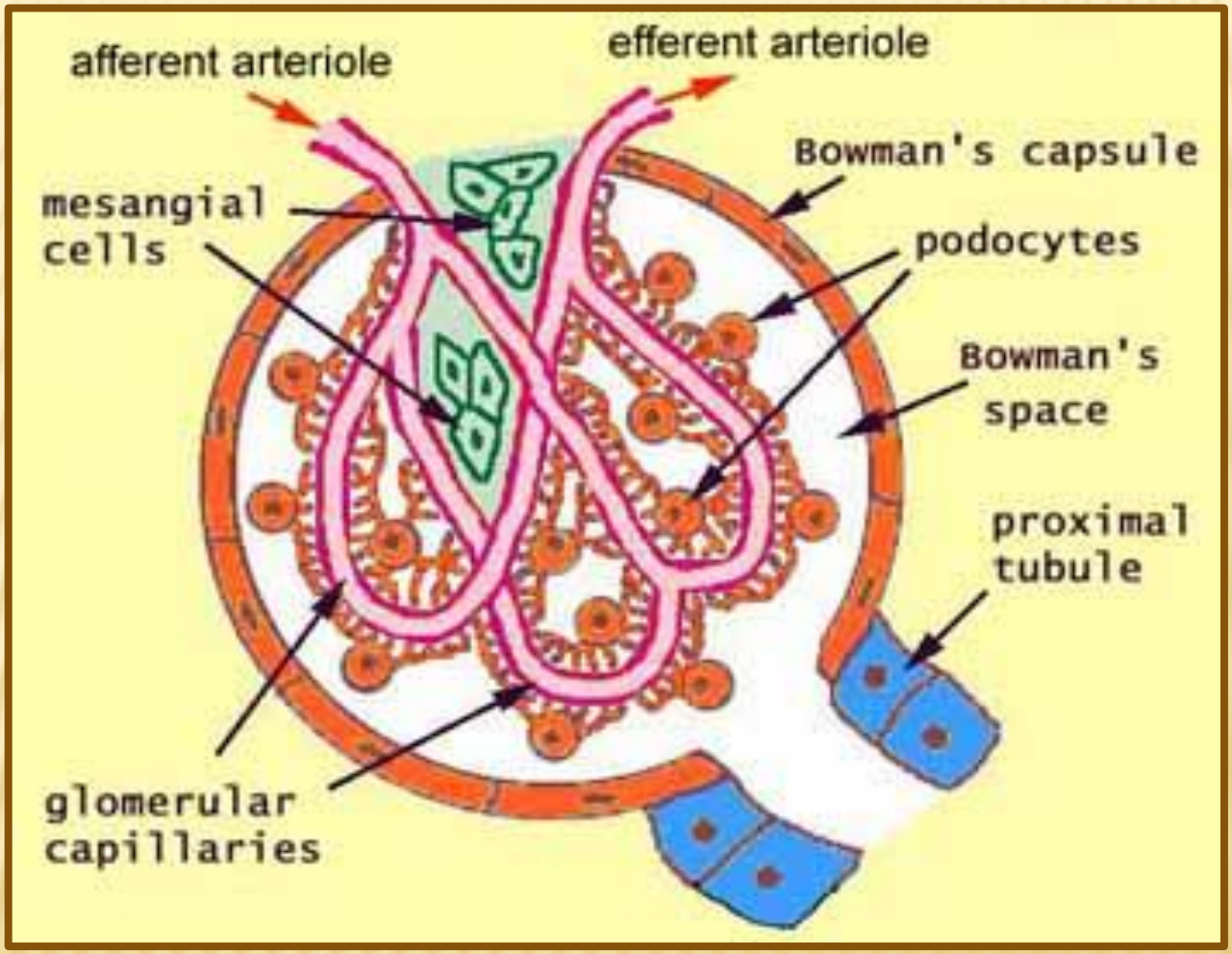
BLOOD SUPPLY



Regional Differences in Nephron Structure: Cortical and Juxtamedullary Nephrons



GLOMERULUS


afferent arteriole
efferent arteriole
Bowman's capsule
mesangial cells
podocytes
Bowman's space
proximal tubule
glomerular capillaries

Juxtaglomerular apparatus

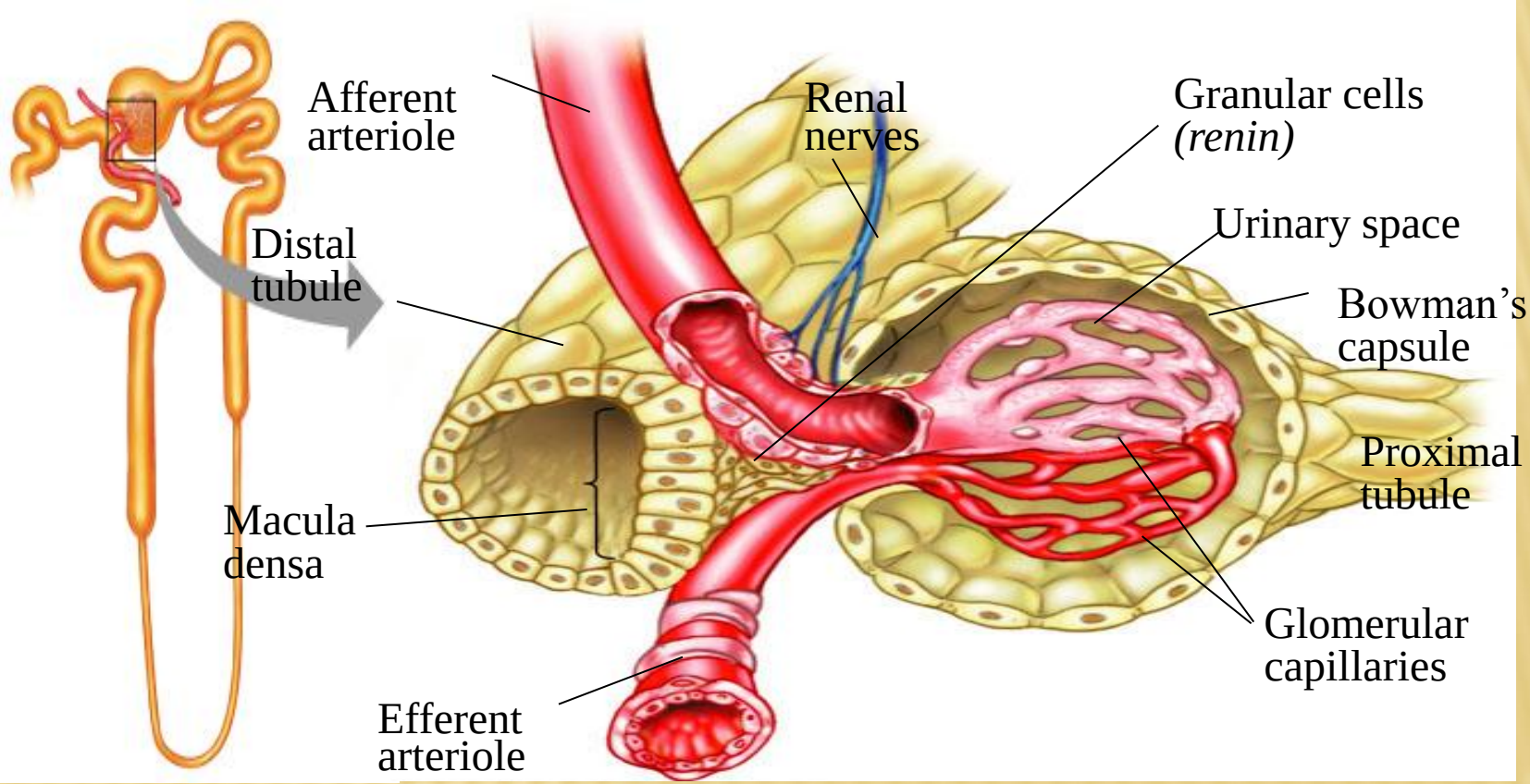
❖ It is formed at the place where distal tubule contacts with afferent arteriole

➢It consists of:

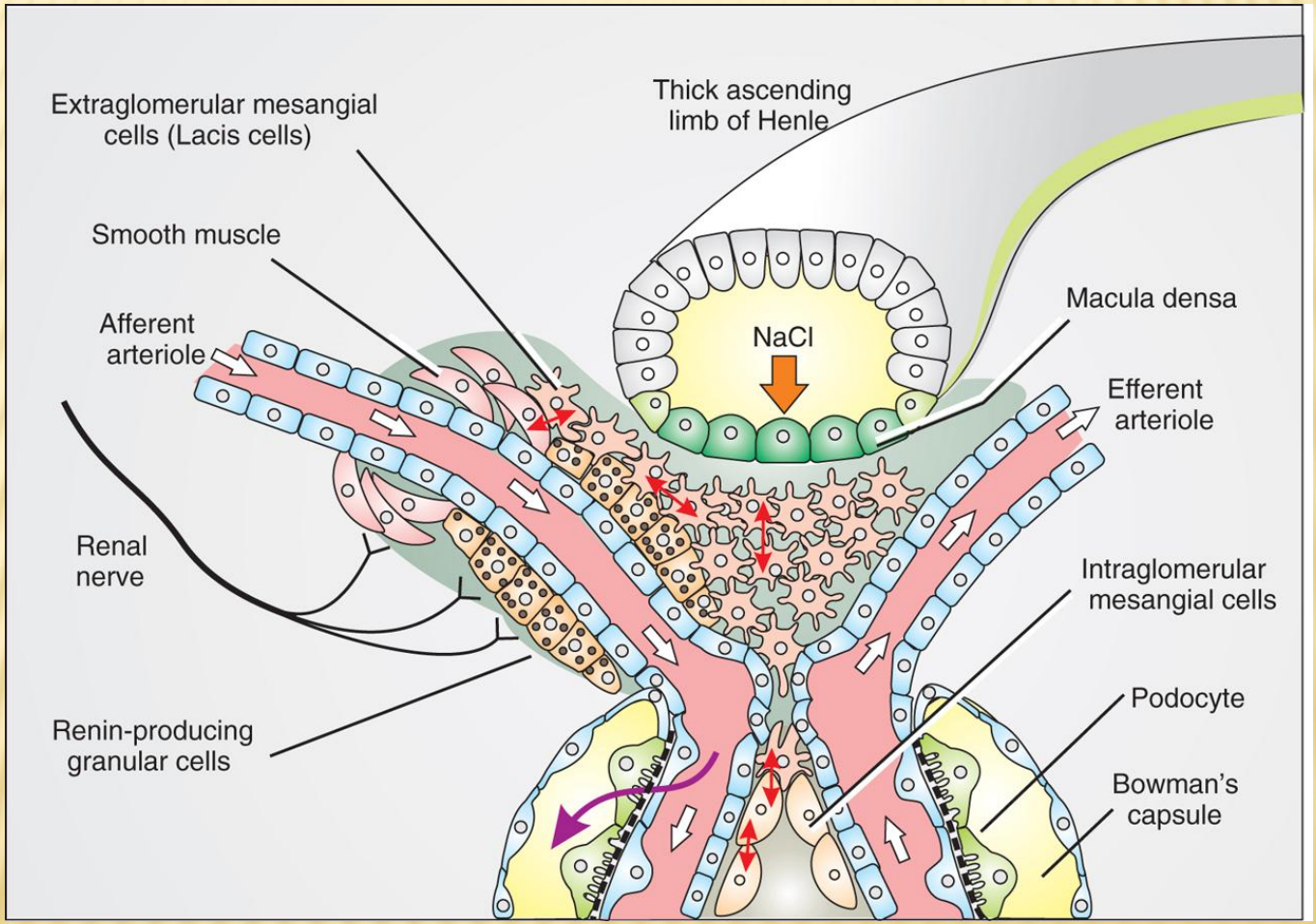
• granular (juxtaglomerular) cells – JG cells are modified smooth muscle cells located *in the walls of the afferent arterioles immediately proximal to the glomeruli, that synthesize renin*

• Macula densa – high dense cells of the distal tubule

• extraglomerular mesangeal cells

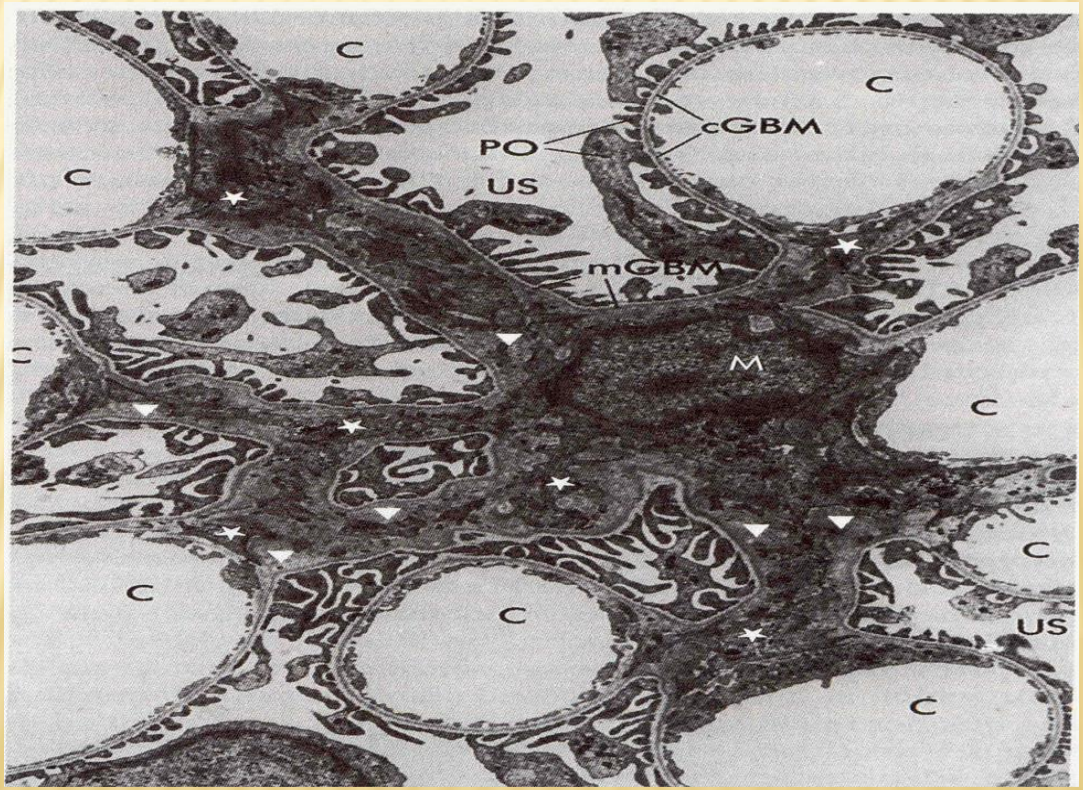


JUXTAGLOMERULAR APPARATUS



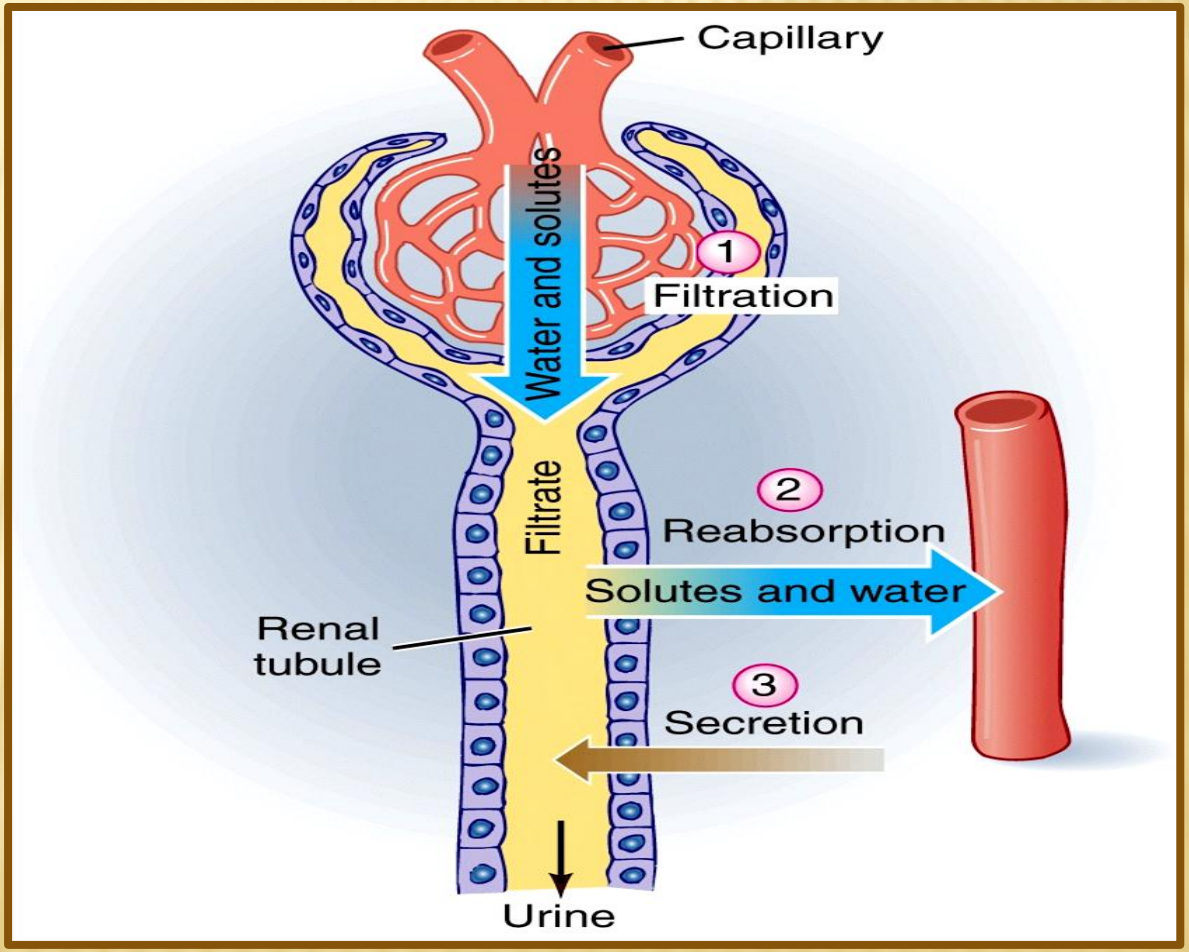
➢*The functions of mesangial cells:*

- ✓supporting
- ✓secretory --> prostaglandins, cytokines
- ✓defensive --> phagocytosis
- ✓regulatory – their contraction controls blood flow and filtration area

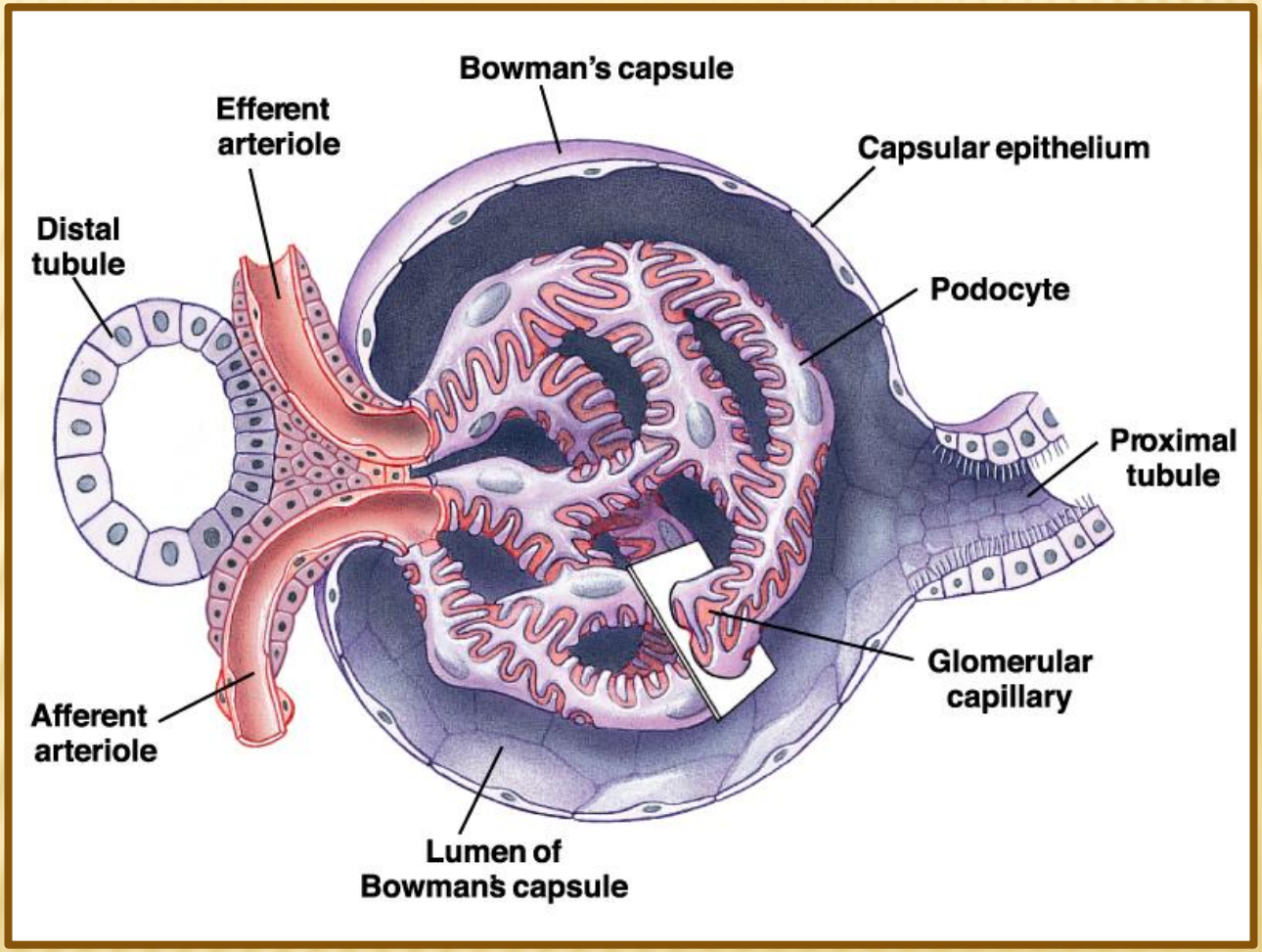


URINE FORMATION RESULTS FROM:

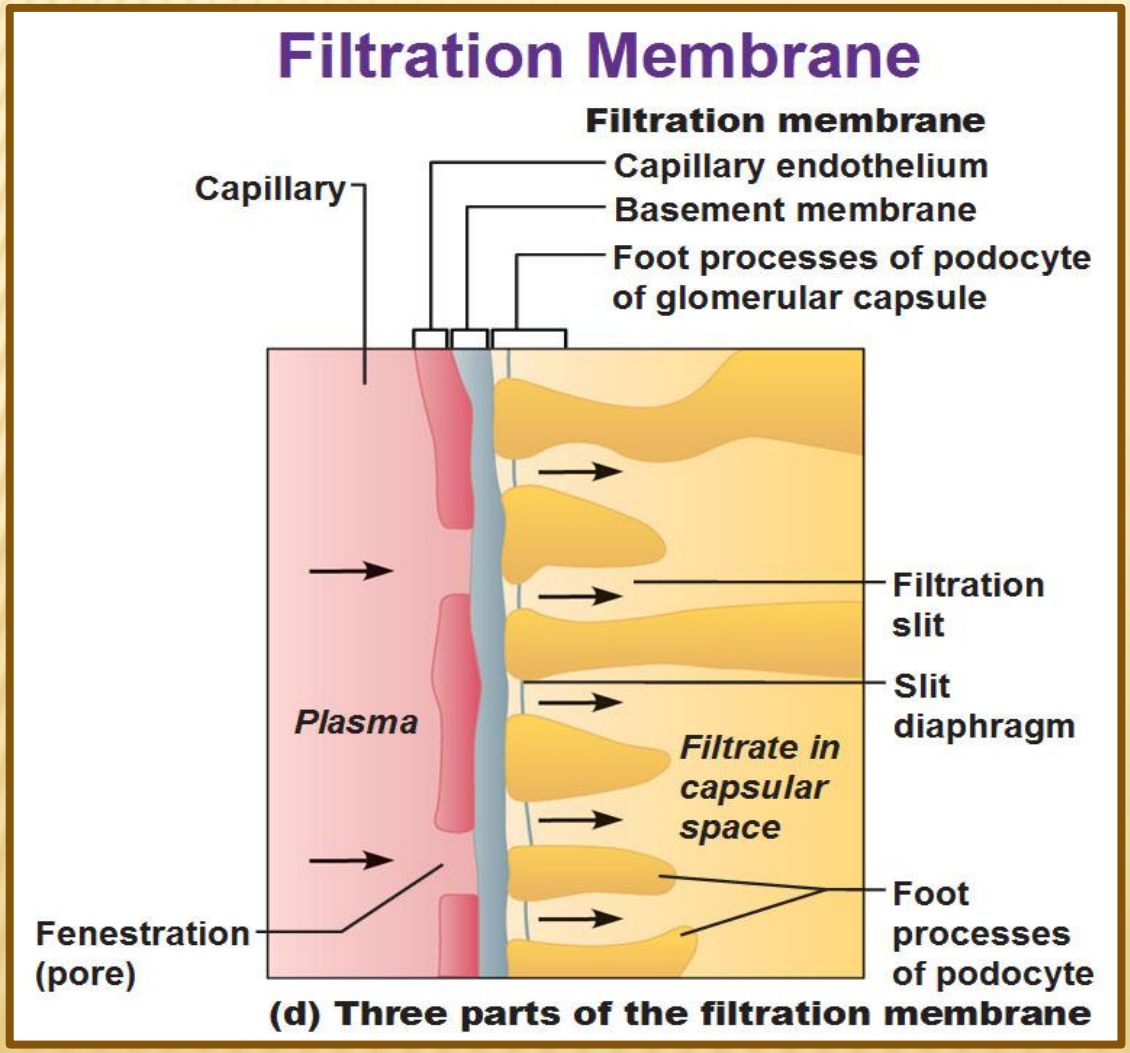
- Glomerular Filtration,
- Tubular Reabsorption, and
- Tubular Secretion

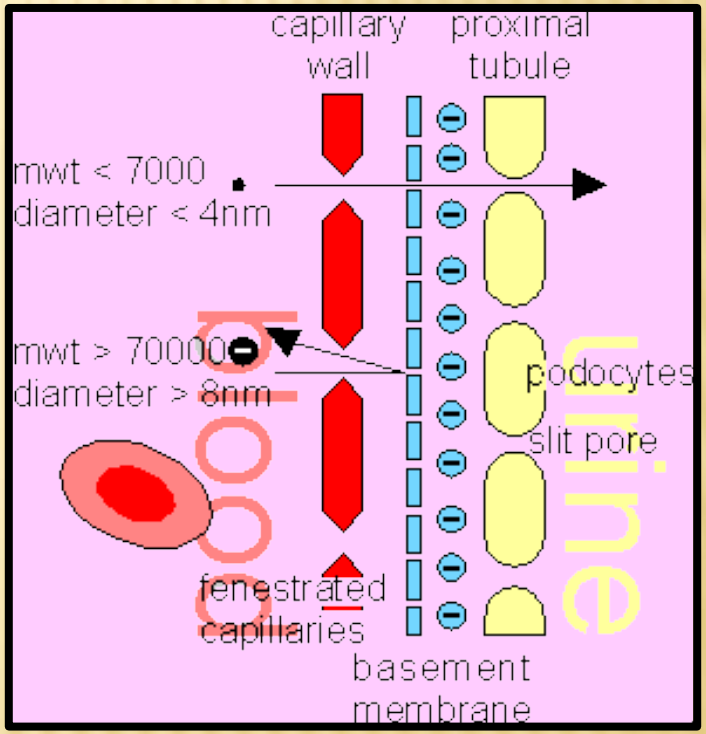


GLOMERULAR FILTRATION



GLOMERULAR FILTRATION MEMBRANE





DETERMINANTS OF THE GLOMERULAR FILTRATION RATE (GFR)

- The GFR is determined by

(1) the sum of the hydrostatic and colloid osmotic forces across the glomerular membrane, which gives the *net filtration pressure, and*

(2) the glomerular capillary filtration coefficient, Kf.

- Expressed mathematically, the GFR equals the product of Kf and the net filtration pressure:

GFR = Kf x Net filtration pressure

- ***The net filtration pressure represents the sum of the hydrostatic and colloid osmotic forces that either favor or oppose filtration across the glomerular capillaries. These forces include:***

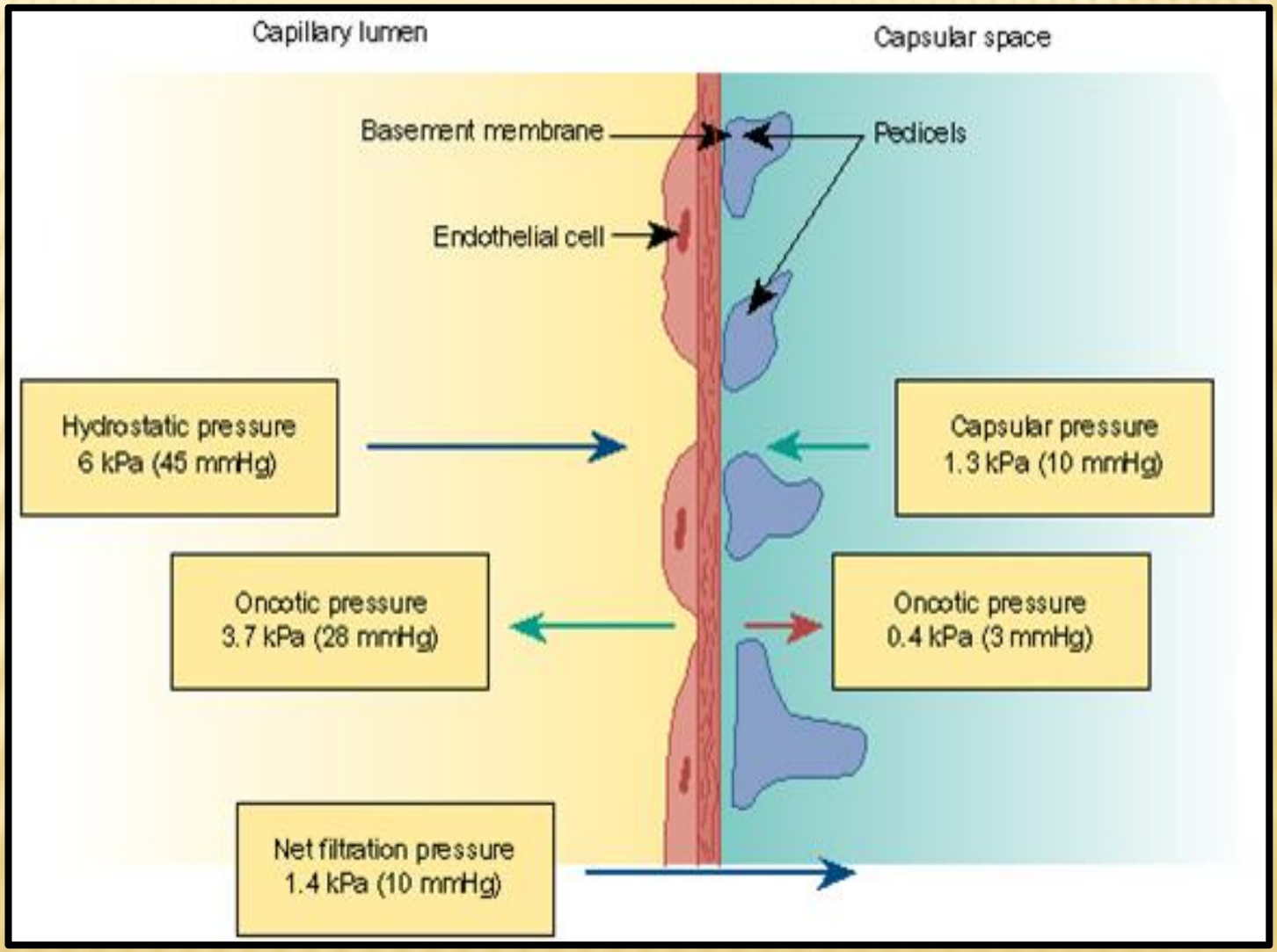
(1) hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, PG), which promotes filtration;

(2) the hydrostatic pressure in Bowman's capsule (PB) outside the capillaries, which opposes filtration;

(3) the colloid osmotic pressure of the glomerular capillary plasma proteins (πG), which opposes filtration; and

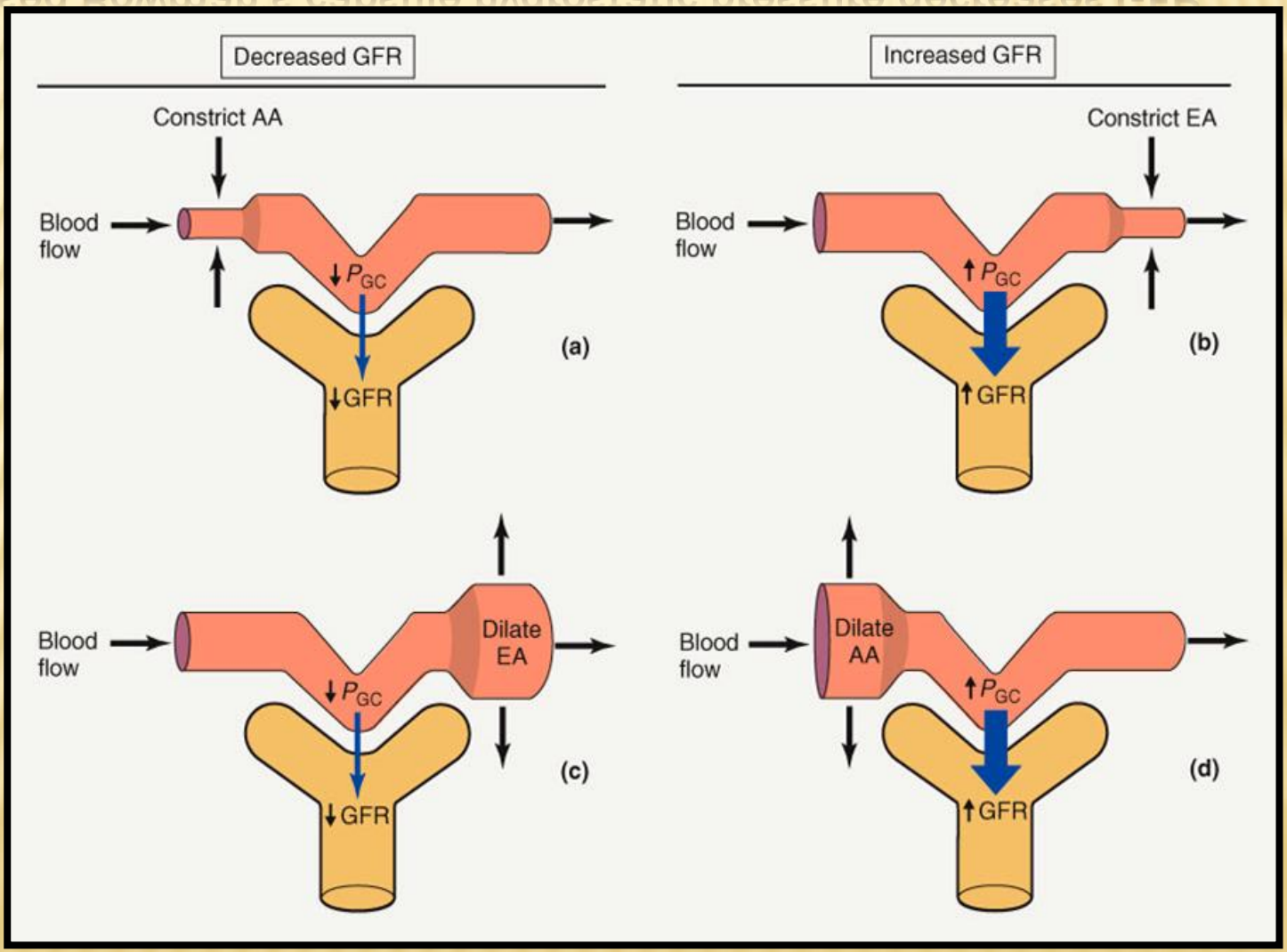
(4) the colloid osmotic pressure of the proteins in Bowman's capsule (πB), which promotes filtration. (Under normal conditions, the concentration of protein in the glomerular filtrate is so low that the colloid osmotic pressure of the Bowman's capsule fluid is considered to be zero.)

THE GLOMERULAR FILTRATION RATE CAN BE EXPRESSED AS GFR = Kf x (PG – PB – πG + πB)

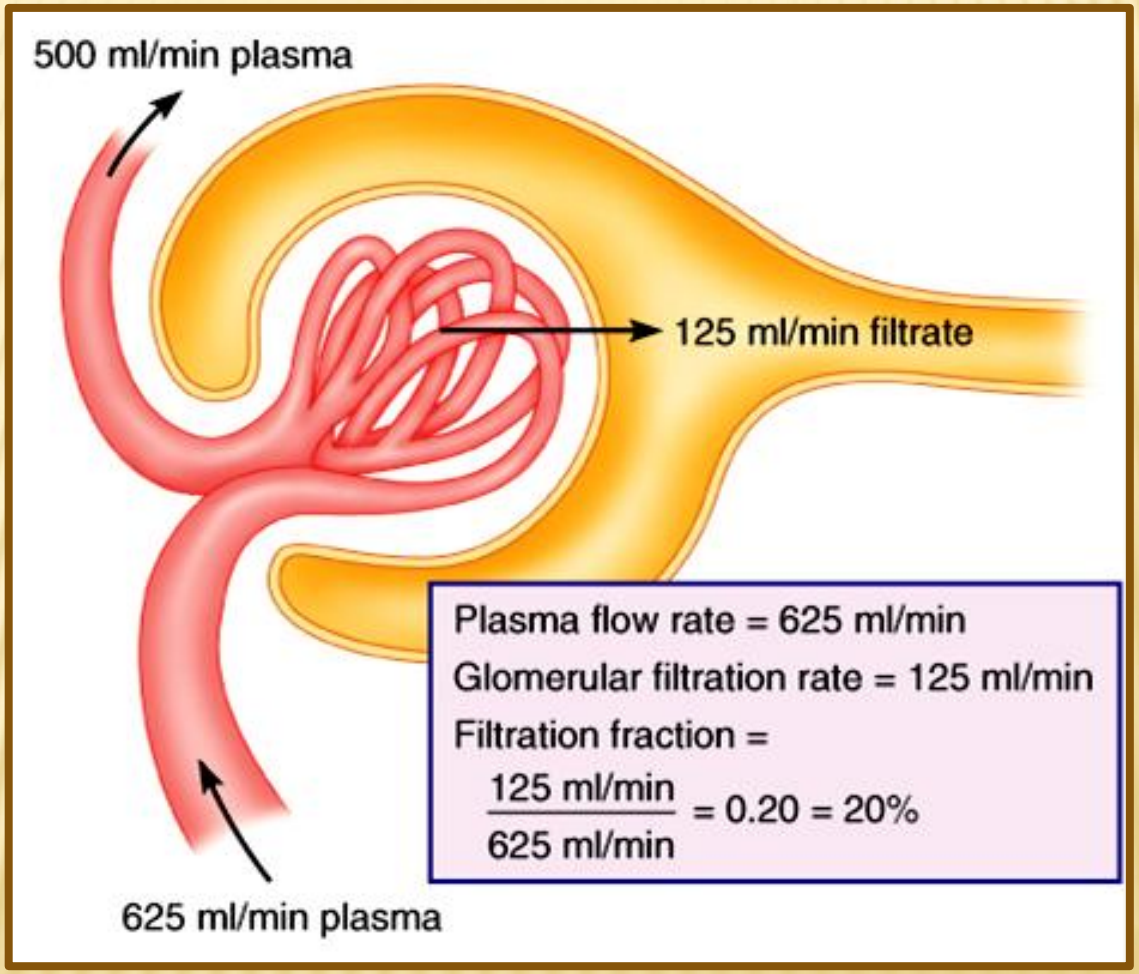


FACTORS ON WHICH GFR DEPENDS :

1. increased glomerular capillary filtration coefficient increases GFR
2. increased glomerular capillary hydrostatic pressure increases GFR
3. increased glomerular capillary colloid osmotic pressure decreases GFR
4. increased Bowman's capsule hydrostatic pressure decreases GFR



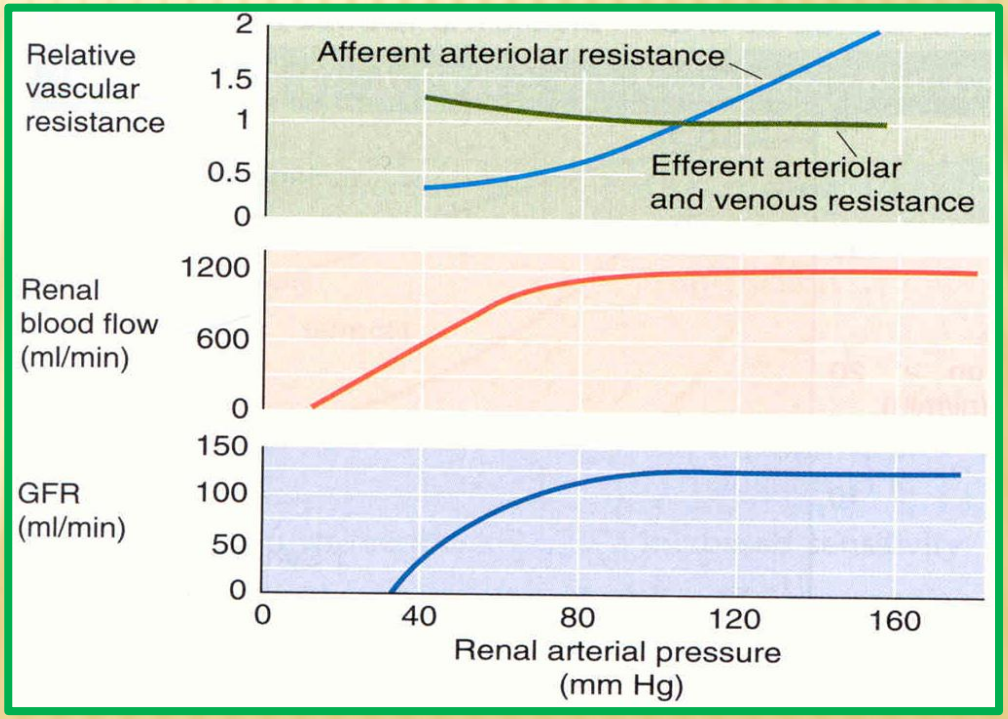
GLOMERULAR FILTRATION RATE



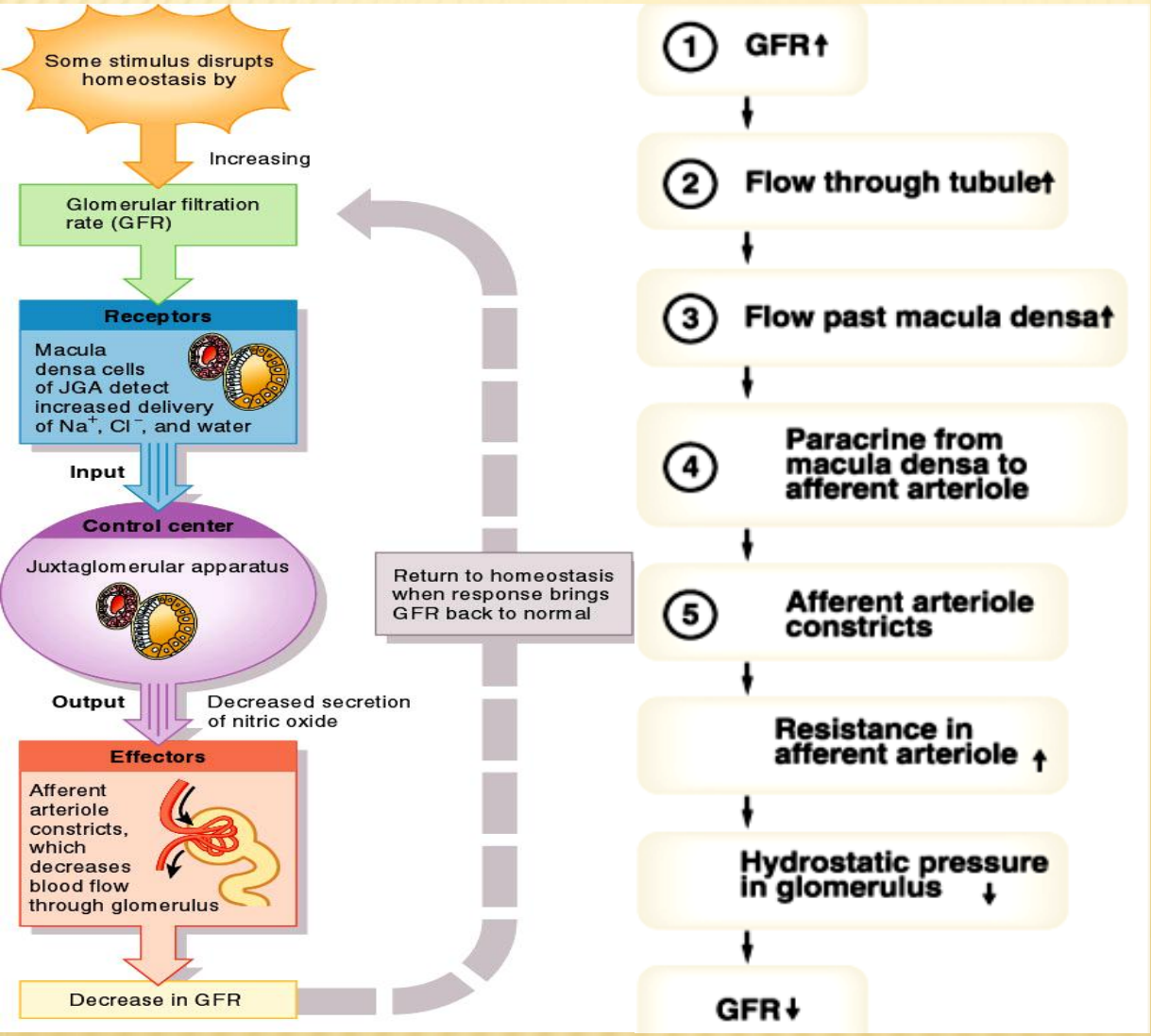
Autoregulation of GFR and Renal Blood Flow

Renal autoregulation prevents large changes in GFR that would otherwise occur when the AP is changed between 80 – 180 mm Hg, using 2 mechanisms:

(1) ***Myogenic Autoregulation of Renal Blood Flow and GFR,*** and
(2) a phenomenon referred to as ***Glomerulotubular balance*** - adaptive mechanisms in the renal tubules that allow them to increase their reabsorption rate when GFR rises.



ROLE OF TUBULOGLOMERULAR FEEDBACK IN AUTOREGULATION OF GFR

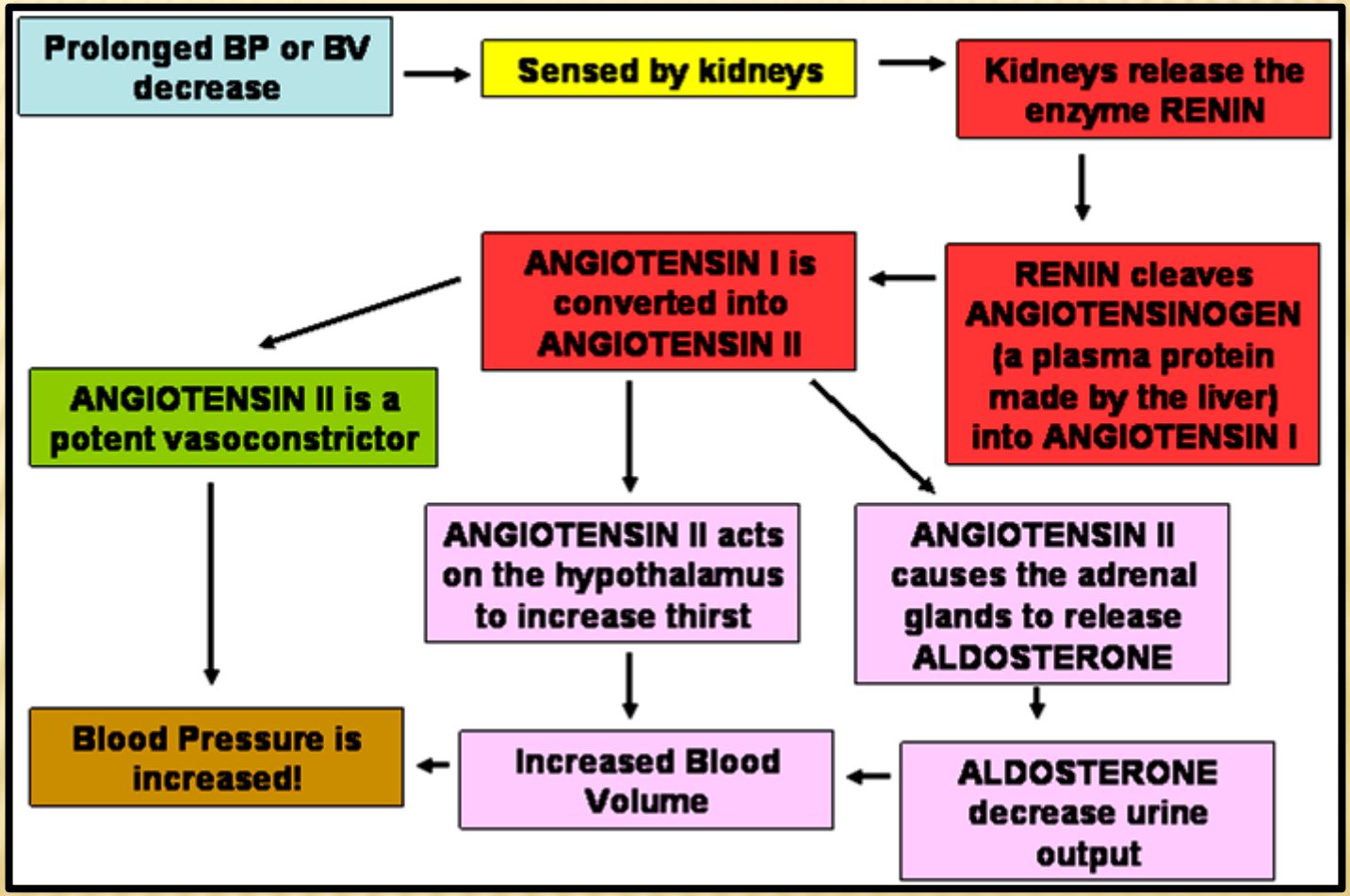


To perform the function of autoregulation, the kidneys have a feedback mechanism that links changes in sodium chloride concentration at the macula densa with the control of renal arteriolar resistance. This feedback helps ensure a relatively constant delivery of sodium chloride to the distal tubule and helps prevent spurious fluctuations in renal excretion that would otherwise occur.

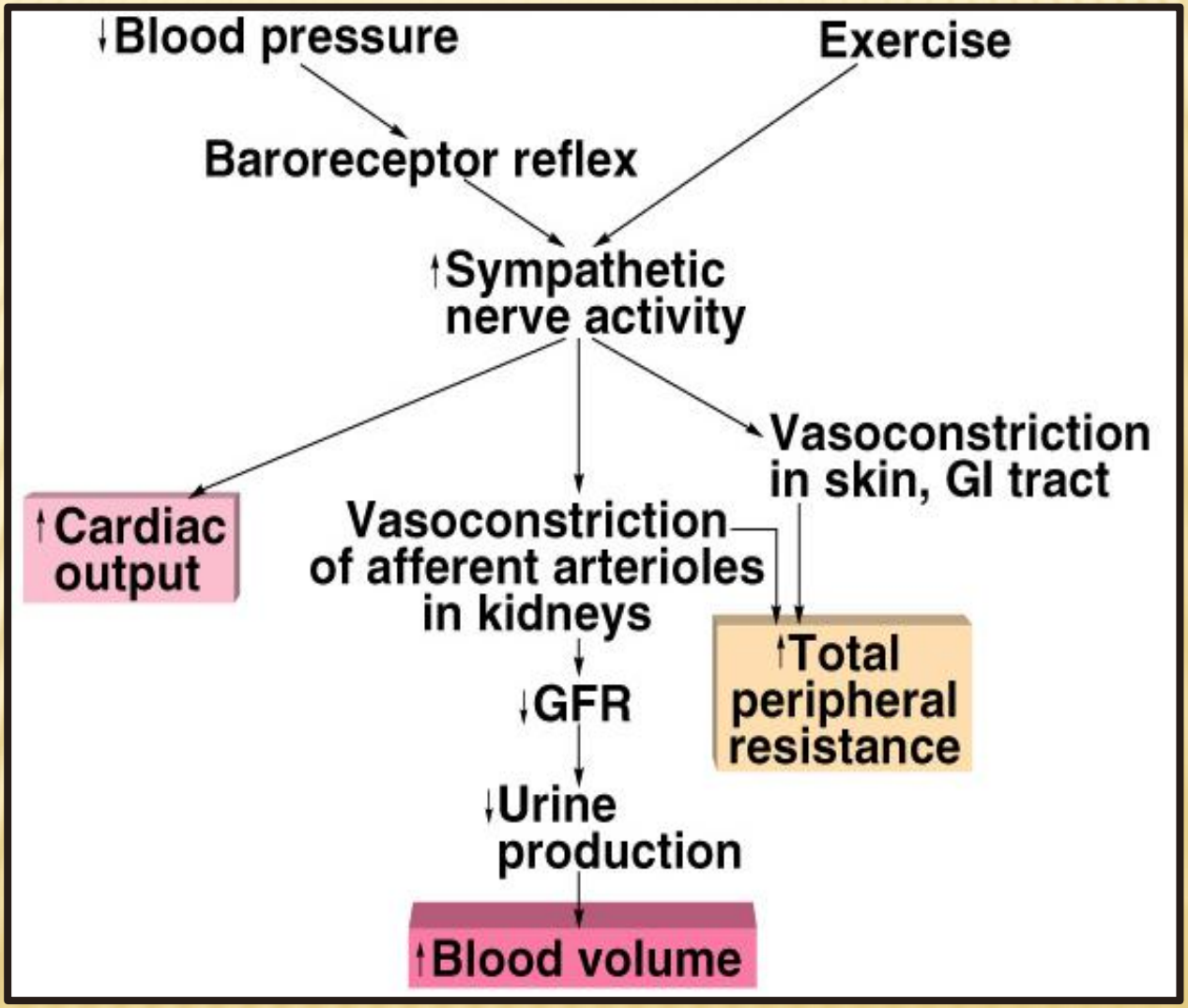
HORMONES AND AUTACOIDS THAT INFLUENCE GLOMERULAR FILTRATION RATE (GFR)

- Norepinephrine ↓
- Epinephrine ↓
- Endothelin ↓
- Angiotensin II (prevents ↓)
- Endothelial-derived nitric oxide ↑
- Prostaglandins ↑
- Bradykinin ↑

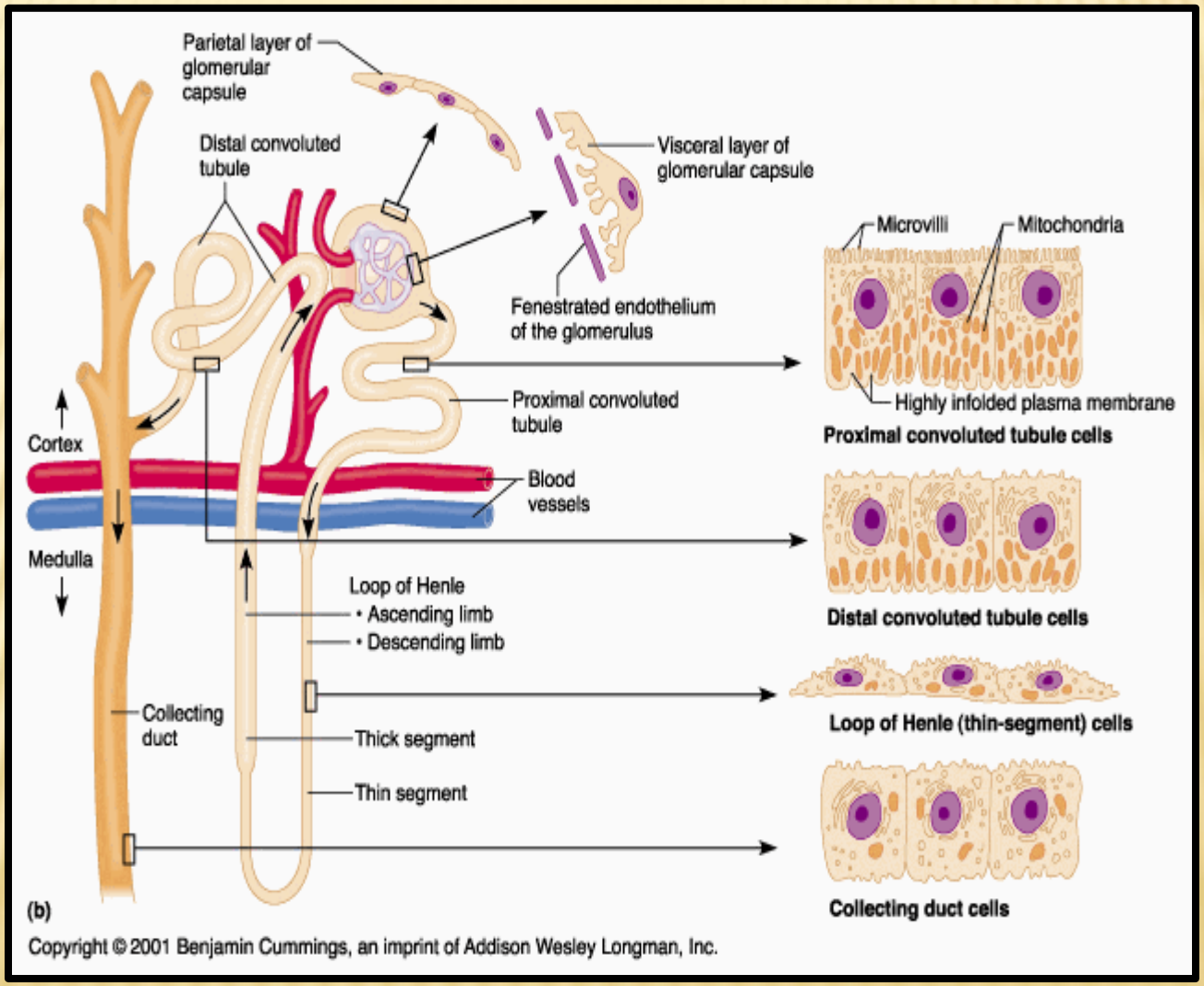
HORMONAL CONTROL OF GFR



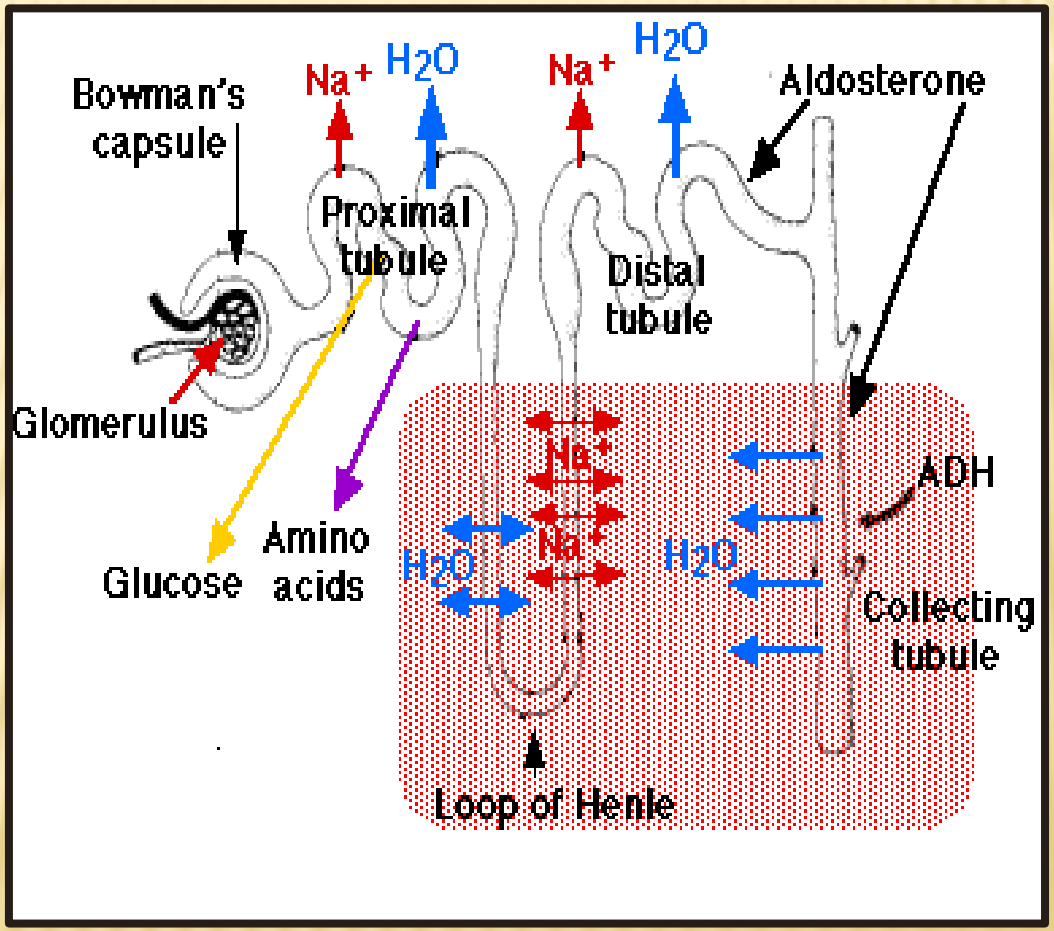
NERVOUS CONTROL OF GFR



EPITHELIUM OF THE TUBULAR SYSTEM



REABSORPTION



REABSORPTION OF SODIUM IONS

- 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 ATP-ase pump on the basolateral side of the membrane.
2. Sodium is transported across the basolateral membrane against an electrochemical gradient by the sodium-potassium ATP-ase pump.

REABSORPTION OF SODIUM IONS

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.

- 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.
- Furthermore, this transport maximum can be increased in response to certain hormones, such as *aldosterone.*

SECONDARY ACTIVE TRANSPORT OF GLUCOSE AND AMINO ACIDS IN THE PROXIMAL TUBULE

- 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 virtually 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.

SECONDARY ACTIVE TRANSPORT OF GLUCOSE AND AMINO ACIDS IN THE PROXIMAL TUBULE

- 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.
- Thus, this 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 transport of sodium.

REABSORPTION AND SECRETION

- Passive Water Reabsorption by Osmosis Is Coupled Mainly to Sodium Reabsorption
- Reabsorption of Chloride, Urea, and Other Solutes by Passive Diffusion
- Reabsorption of potasium by active transport
- Reabsorption of calcium by active transport

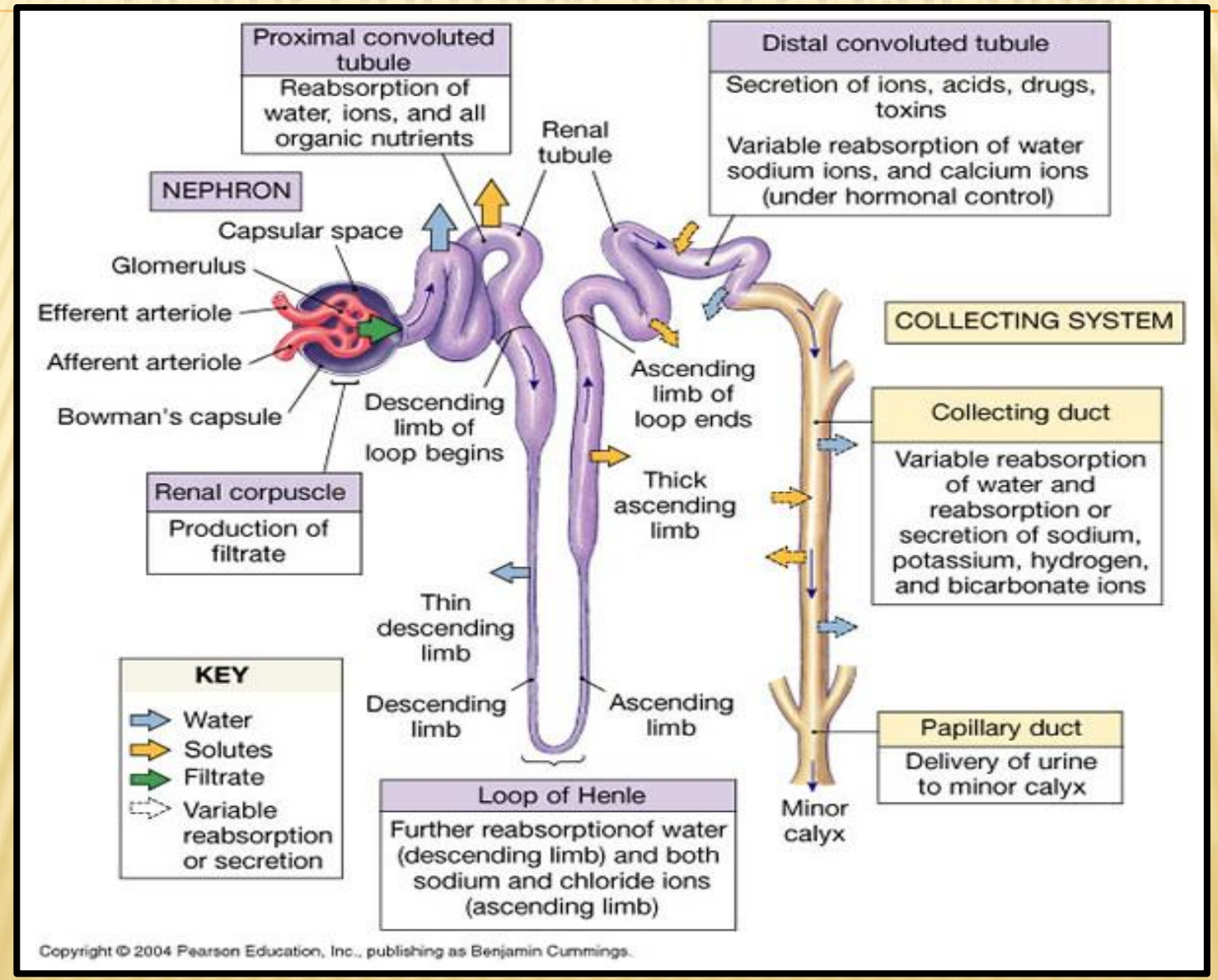
> Reabsorption of water in the collecting tubules is controlled by ADH

> Reabsorption of sodium and secretion of potasium ions in the distal and collecting tubules is controlled by aldosteron

> Reabsorption of calcium ions in the collecting tubules is controlled by parathormone

> Secretion of hydrogen ions along whole tubular system

REABSORPTION AND SECRETION



REGULATION OF TUBULAR REABSORPTION

- Glomerulotubular Balance - The Ability of the Tubules to Increase Reabsorption Rate in Response to Increased Tubular Load
- Peritubular Capillary and Renal Interstitial Fluid Physical Forces
- Effect of Arterial Pressure on Urine Output - The Pressure-Natriuresis and Pressure-Diuresis Mechanisms
- Hormonal Control of Tubular Reabsorption (ADH, Aldosterone, Angiotensin II, Parathyroid hormone, Atrial natriuretic peptide)
- Sympathetic Nervous System Activation Increases Sodium Reabsorption

USE OF CLEARANCE METHODS TO QUANTIFY KIDNEY FUNCTION

- The ***renal clearance*** *of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time.*
- This is somewhat of an abstract concept because there is no single volume of plasma that is completely cleared of a substance.
- The concept of renal clearance is based on the principle of mass balance. The renal artery is the single input to the kidney, whereas the renal vein and ureter constitute the two output routes.

RENAL CLEARANCE

- Maintaining mass balance the following relationship can be derived:

$$P_{ax} \cdot RPF_a = (P_{vx} \cdot RPF_v) + (U_x \cdot V)$$

where

P_{ax} and P_{vx} = concentration of substance **X** in the renal artery and renal vein plasma

RPF_a and RPF_v = renal plasma flow rates in the artery and vein

U_x = concentration of **X** in the urine

V = urine flow rate per minute

- The principle of **renal clearance (C_x)** emphasizes the excretory function of the kidney; it considers only the rate at which a substance is excreted into the urine and not the rate at which it is returned to the systemic circulation in the renal vein. Therefore in terms of mass balance, the urinary excretion rate of **X** **(U_x . V)** is proportional to the plasma concentration of **X (P_{ax}).**
- To equate the urinary excretion rate of **X** to its renal arterial plasma concentration one must determine the rate at which **X** is removed from the plasma by the kidneys. This removal rate is the clearance **(C_x).**
- $P_{ax} \cdot C_x = U_x \cdot V$
- $C_x = U_x \cdot V / P_x$
- C_x = ml / min and P_x = mg / ml
- V = ml / min and U_x = mg / ml

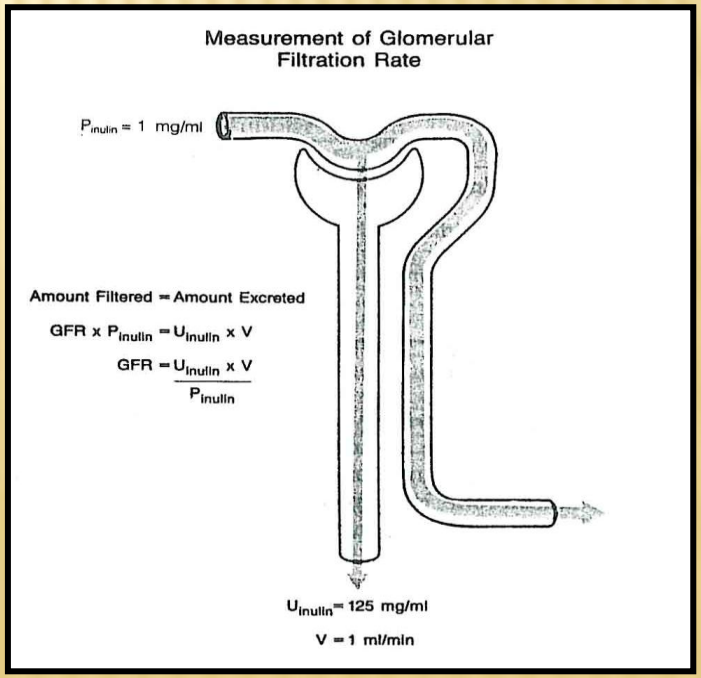
GLOMERULAR FILTRATION RATE (GFR) AND CLEARANCE OF INULIN (C_{IN})

- **Inulin** is a polyfructose molecule (m.w. = 5000) that can be used to measure the **GFR**. It is not produced endogenously by the body and therefore must be administered intravenously. Inulin is freely filtered at the glomerulus and neither reabsorbed, secreted nor metabolized by the cells of the nephron. The amount of inulin excreted in the urine per minute equals the amount of inulin filtered at the glomerulus each minute:

amount filtered = amount excreted

$$GFR \cdot P_{in} = U_{in} \cdot V$$

$$GFR = U_{in} \cdot V / P_{in}$$



- Any substance that meets the following criteria will serve as an appropriate marker for the measurement of GFR:

1. The substance must be nontoxic.
2. The substance must not bind on plasma proteins.
3. The substance must be freely filtered by the glomerulus.
4. The substance must not be reabsorbed or secreted by the nephron.
5. The substance must not be metabolized or produced by the kidney.
6. The substance must not alter GFR.

- The fact that inulin must be infused intravenously limits its use in clinical settings. Consequently **Creatinine** is used to estimate the GFR. It is a by-product of skeletal muscle creatine metabolism. However creatinine is not a perfect substance to measure GFR, because it is secreted in the proximal tubule when its plasma concentration is greater than 0.02 mg / ml. The creatinine is present in the plasma at a relatively constant concentration and for this reason C_{cr} is the most widely used method of estimating GFR clinically.

  GFR is proportional to body surface area and the clearance of each substance must multiply by **coefficient K = 1.73 / BSA .**

  1.73 m^2 = standard body surface area of 25 years old human

  BSA = m^2 body surface area of the patient

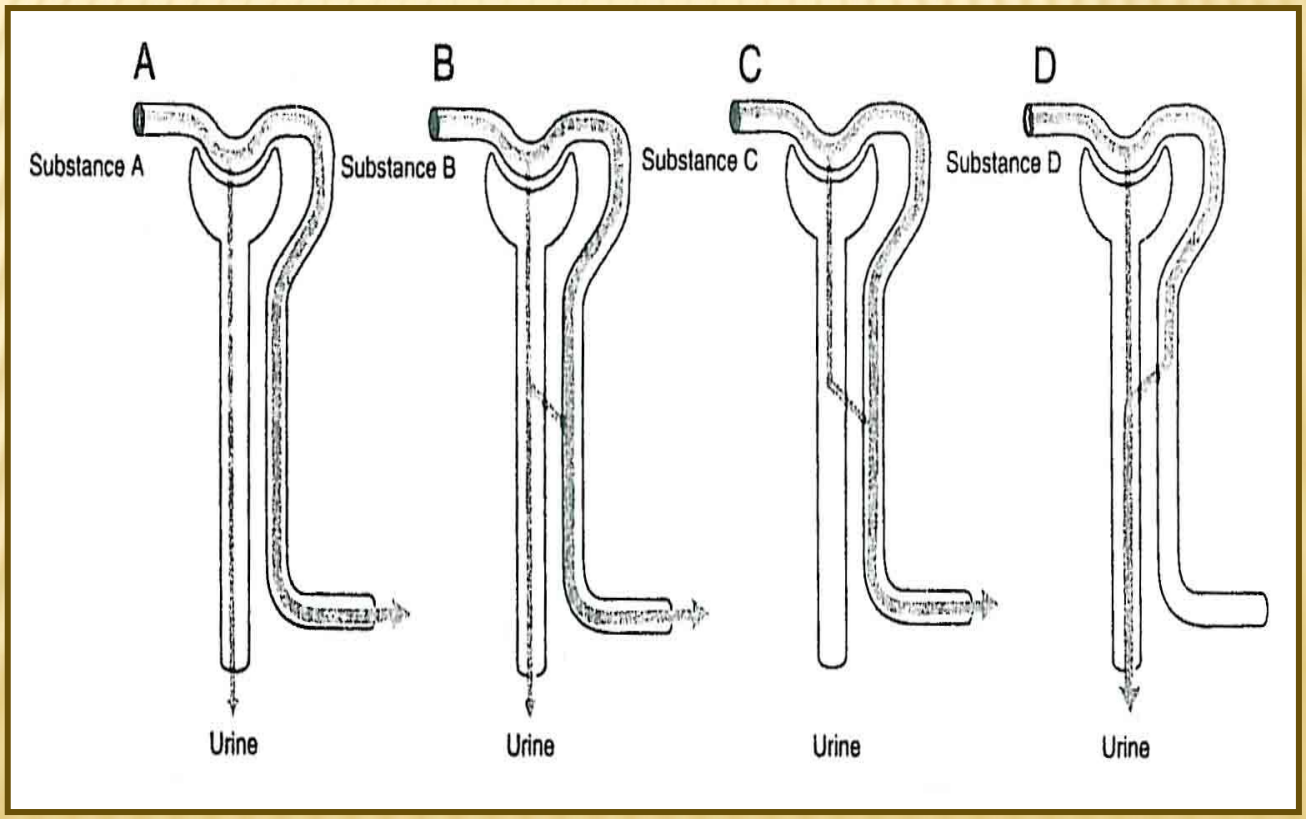
- **Normal value of GFR for standard body surface area:**

  C_{in} = 100 - 150 ml /min ; av. C_{in} = 125 ml /min

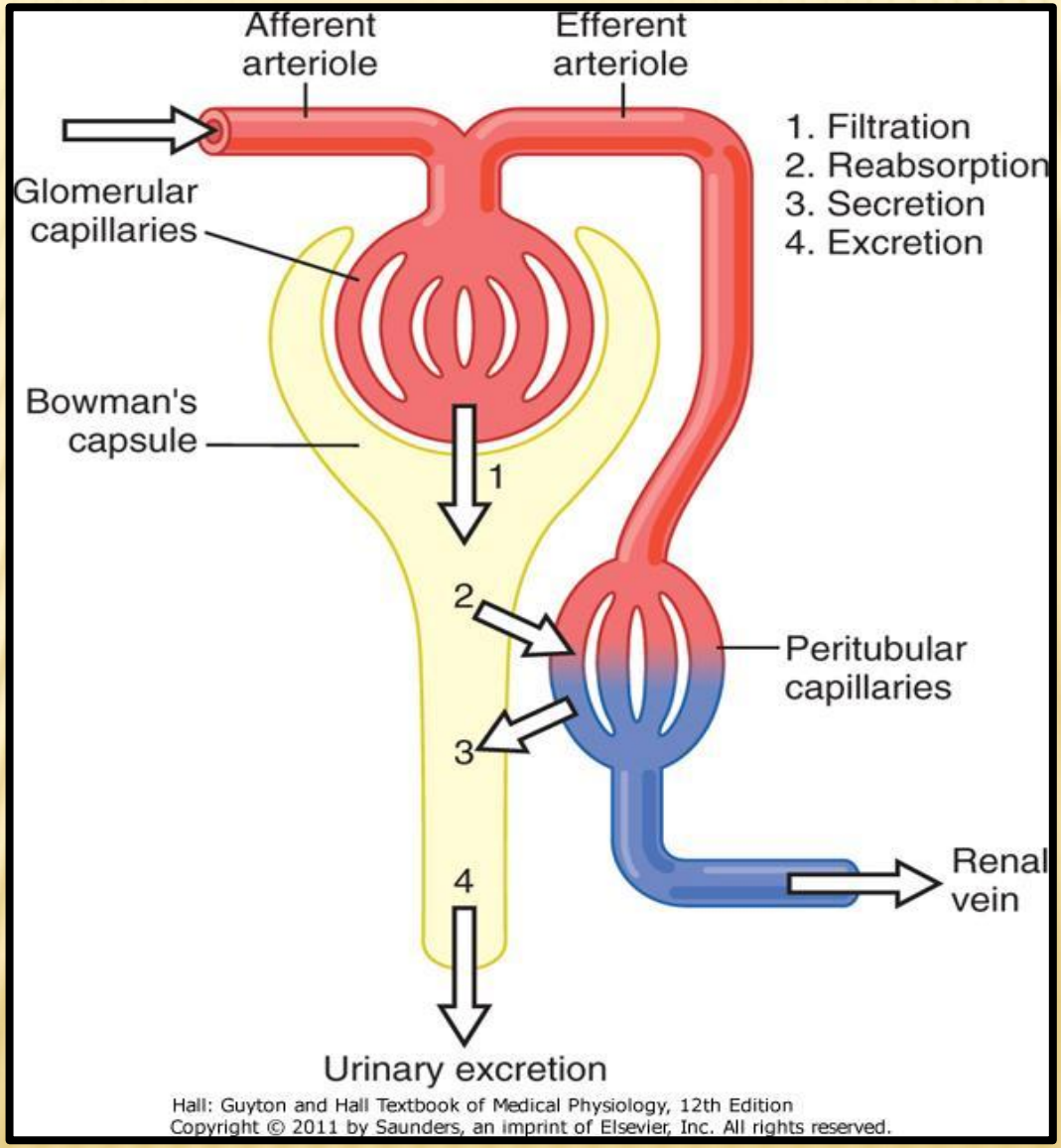
  C_{cr} = 80 - 180 ml /min

- ***Most substances are filtered and either reabsorbed or secreted***

1. If its clearance is less than that of Cin, the substance is reabsorbed by the nephron.
2. If its clearance is greater than that Cin, the substance is secreted.
3. If its clearance equals that Cin, the substance is only filtered.



URINARY EXCRETION = GLOMERULAR FILTRATION – TUBULAR REABSORPTION + TUBULAR SECRETION



PAH CLEARANCE

- p-Aminohippuric acid (PAH) is an organic anion excreted into the urine by the processes of glomerular filtration and tubular secretion. As inulin, PAH is not produced in the body and therefore must be infused.

$$C_{PAH} = U_{PAH} \cdot V / P_{PAH}$$

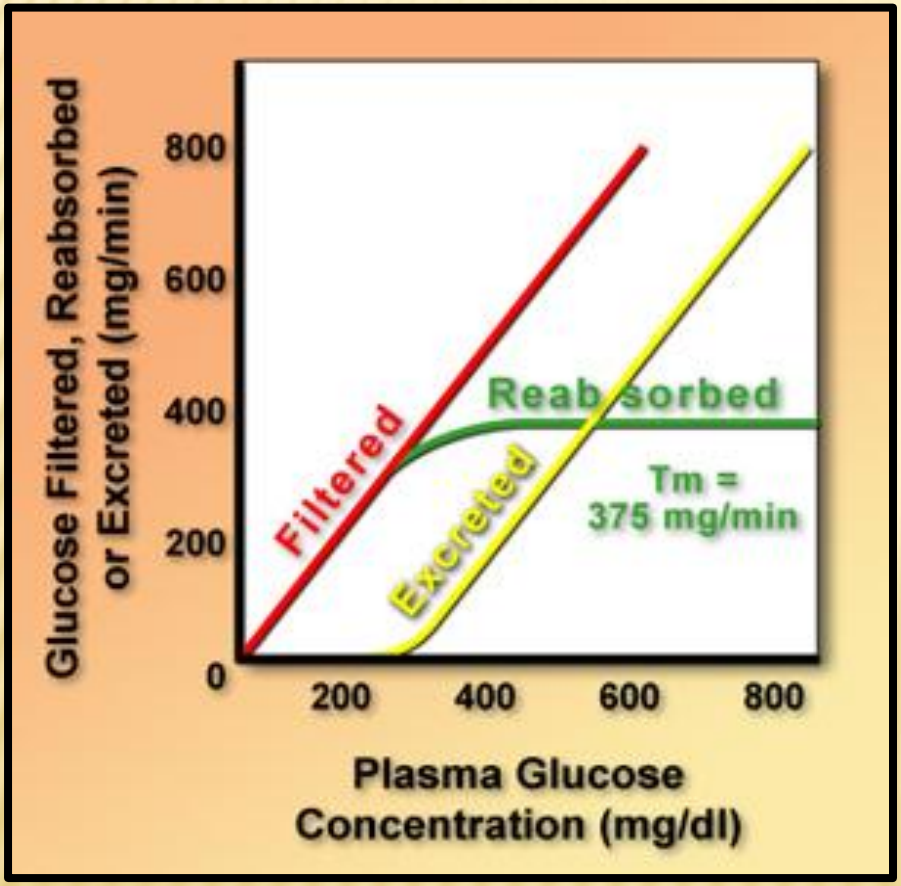
Normal value of C_{PAH} for standard body surface area:

$C_{PAH} = 500 - 800$ ml / min ;

C_{PAH} = av. 650 ml / min

TRANSPORT MAXIMUM FOR SUBSTANCES THAT ARE ACTIVELY REABSORBED

$$T_{max\ gl} = C_{in} \cdot P_{gl} - U_{gl} \cdot V$$

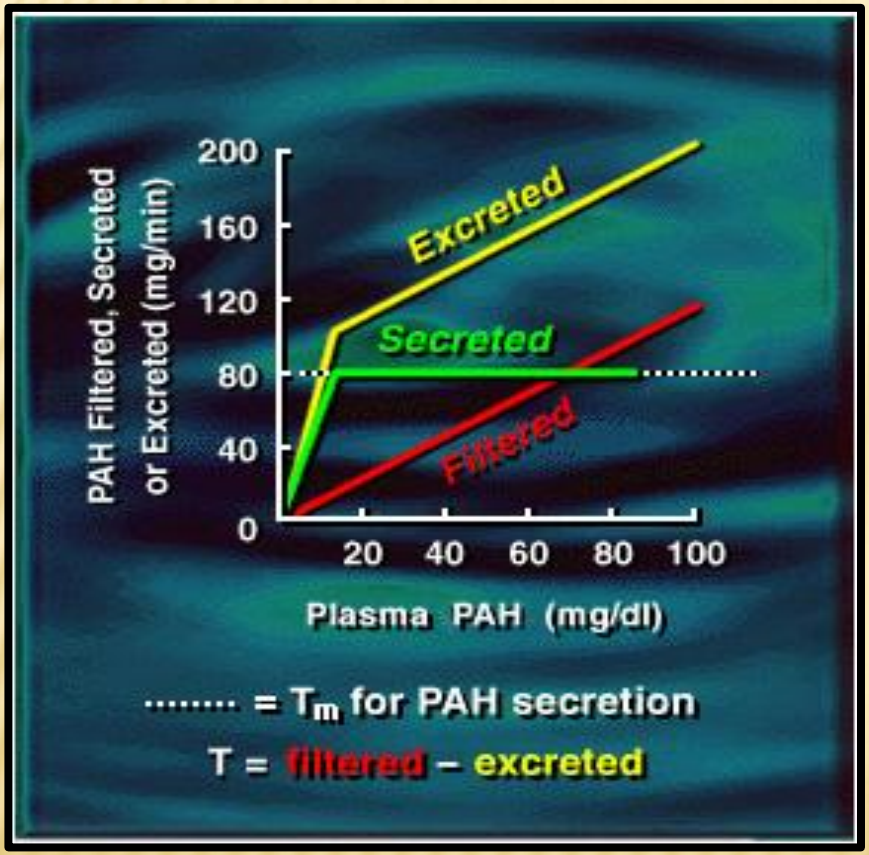


We can use clearance method for determining $T_{max\ gl}$ and $S_{max\ PAH}$. For most substances that are actively reabsorbed or secreted, there is a limit to the rate at which the solute can be transported. It is due to saturation of the specific transport systems. The glucose transport system in the proximal tubule is a good example. The $T_{max\ gl}$ varies from individual to individual and normally in adult human averages about 320 mg / min (300 - 375 mg / min). When P_{gl} is normal C_{gl} = 0, because whole filtered glucose is reabsorbed. The plasma glucose concentration at which glucose first appears in the urine is called the plasma threshold (P_{gl} = 10 mmol/l). Beyond this point the excretion rate increases linearly and parallels the filtered load.

TRANSPORT MAXIMUMS FOR SUBSTANCES THAT ARE ACTIVELY SECRETED

$S_{max\ PAH} = U_{PAH} \cdot V - C_{in} \cdot P_{PAH}$

$S_{max\ PAH}$ - normal average value of 80 mg / min



At a constant GFR the filtered load of PAH increases linearly whit the increase in plasma PAH concentration. The secretion process becomes saturated between P_{PAH} of 0,1 and 0,2 mg / ml. Below the $S_{max\ PAH}$ virtually all of the PAH that enters the kidney is excreted, thus clearance of PAH can be used to measure the renal plasma flow (**RPF**). Approximately 90 % of plasma does in fact flow through peritubular capillaries that surround the proximal tubules (**effective renal plasma flow - ERPF**). However 10 % perfuse some of the medullary structures, the renal capsule and part of the renal hilum. Thus the PAH in this plasma can not be secreted and this portion of PAH is returned to the systemic circulation in the renal vein plasma

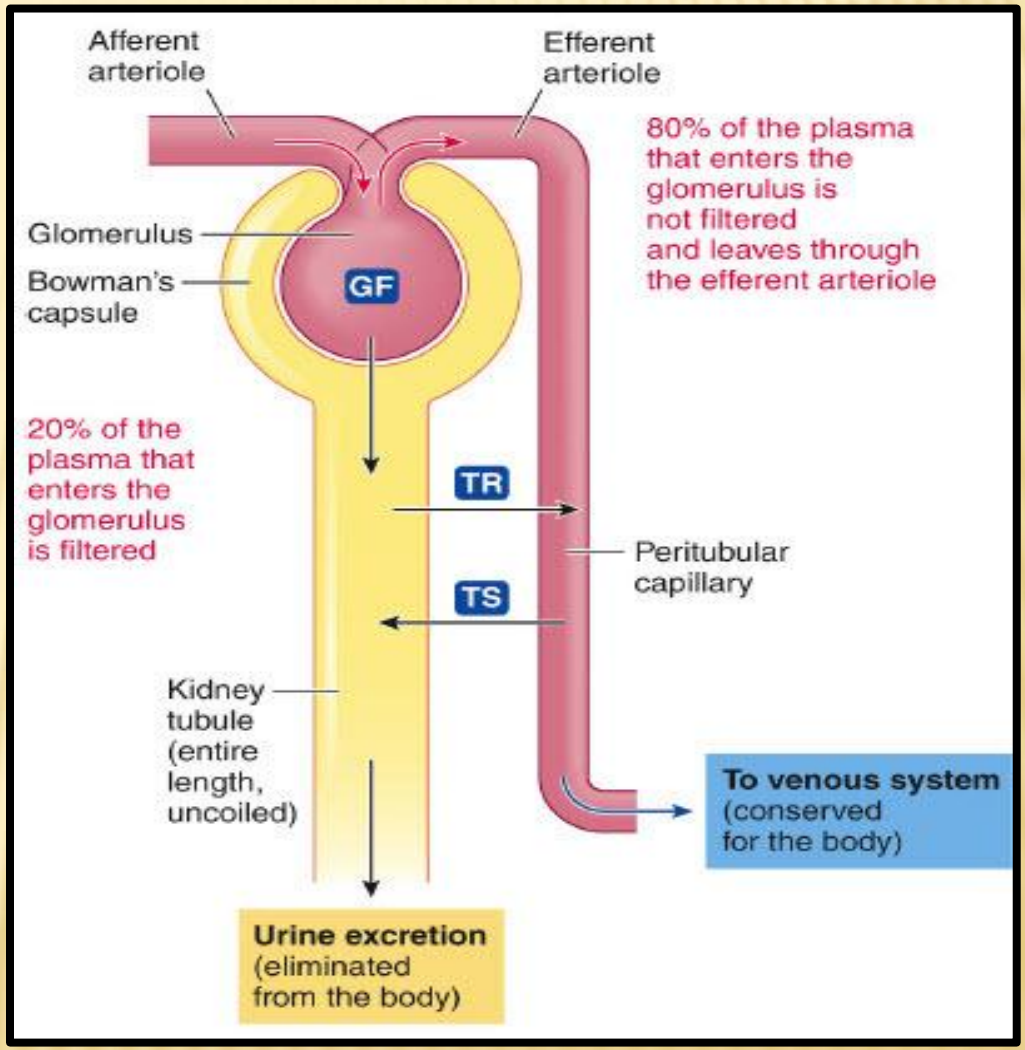
- **ERPF = C_{PAH}**
- ERPF - 90% T RPF= ERPF . 100 / 90
- TRPF - 100% T RPF= **ERPF / 0.9**
- The **C_{PAH} also can be used to estimate the renal blood flow (RBF).** Whole blood consists of a cellular fraction (Hematocrit) and a plasma fraction (1- Hct). Once the Hct is known, TRBF can be calculated as
- **TRBF = TRPF / 1 - Hct**
- **RBF normal av. value = 1200 ml / min**

FILTRATION FRACTION (FF) -
THE PORTION OF PLASMA THAT IS FILTERED PASSING TROUGH THE NEFRONS

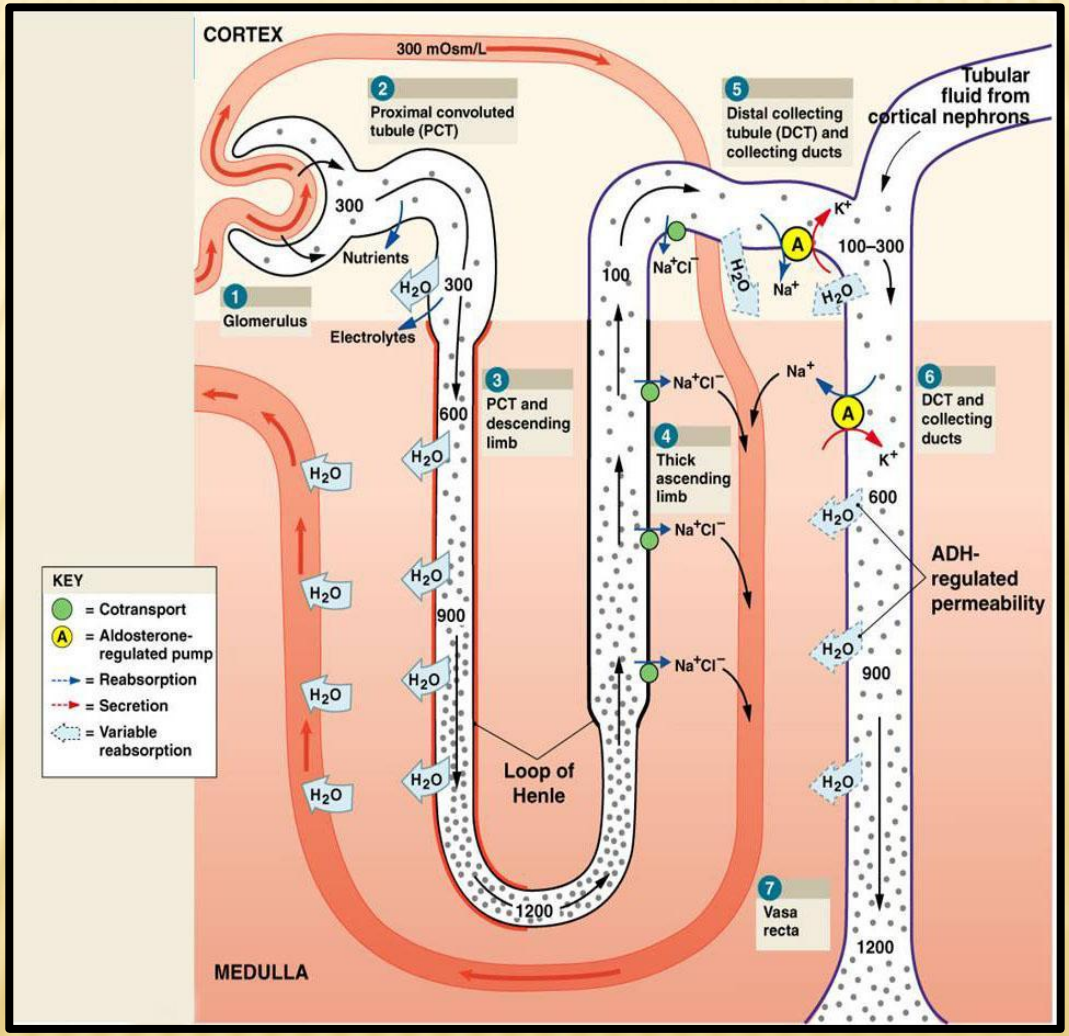
FF = GFR .100 / ERPF

FF = C_{in} . 100 / C_{pah}

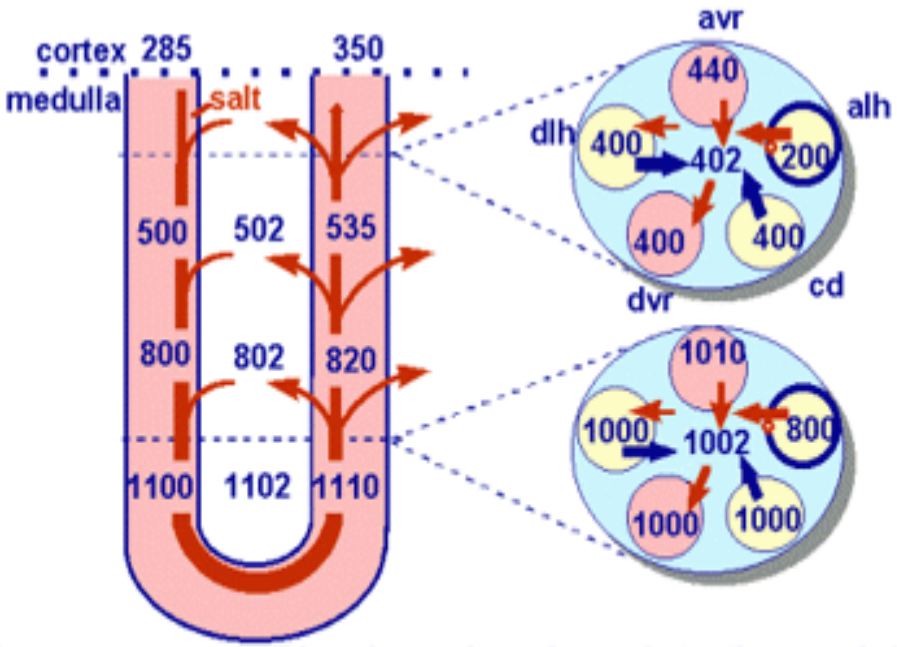
normal av. value of FF = 20%



CONCENTRATION AND DILUTION OF URINE

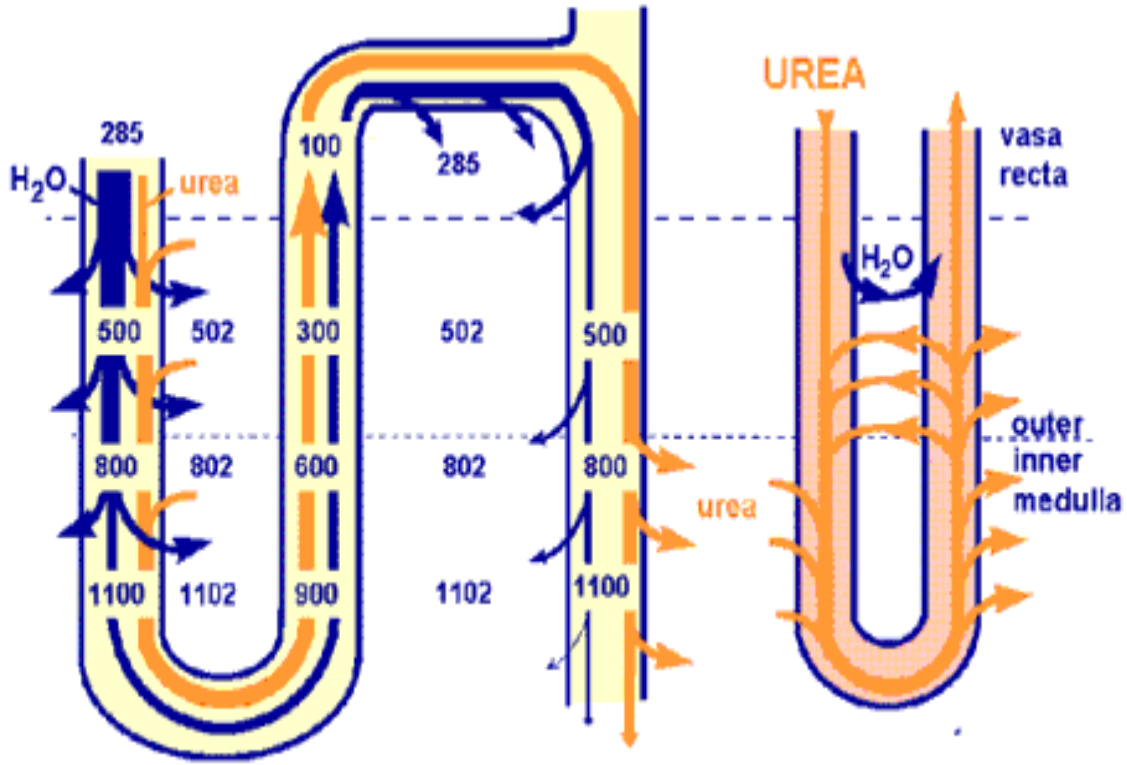


THE COUNTERCURRENT EXCHANGER: THE VASA RECTA



- **Descending vasa recta:** Blood coming down into the medulla from the cortex comes into contact with the concentrated medullary ISF. Salt diffuses from that ISF into the blood increasing the plasma conc.
- **Ascending vasa recta:** Concentrated blood flowing up towards the cortex from the papilla loses salt to the more dilute medullary ISF.
- Thus salt, reabsorbed from the loop of Henle, is trapped and recycled within the medulla by countercurrent flow of blood in the vasa recta.

COUNTERCURRENT CONCENTRATION OF UREA



- **Vasa recta:** Blood flowing into the medulla picks up urea from the concentrated medullary ISF. As that concentrated blood flows up from the papilla it loses urea to the medullary ISF.
- **Urea,** reabsorbed from the collecting tubule, is thus recycled and trapped within the medulla.

MICTURITION

- Micturition is the process by which the urinary bladder empties when it becomes filled.
- This involves two main steps:
- First, the bladder fills progressively until the tension in its walls rises above a threshold level; this elicits
- the second step, which is a nervous reflex called the *micturition reflex that empties the bladder or, if this* fails, at least causes a conscious desire to urinate.
- Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or facilitated by centers in the cerebral cortex or brain stem.

MICTURITION REFLEX

- It is stretch reflex initiated by *sensory stretch receptors in the bladder wall, especially* by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures.
- Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the *pelvic nerves and then reflexively back* again to the bladder through the *parasympathetic nerve fibers by way of these same nerves.*
- The micturition reflex is a completely autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain. These centers include

  (1) strong *facilitative and inhibitory centers in the brain stem, located mainly in the pons, and*

  (2) several centers located in the cerebral cortex that are mainly inhibitory but can become excitatory.

MICTURITION REFLEX