RENAL PHYSIOLOGY 1

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Kidney & Body fluids

The kidneys have major homeostatic functions:

1-Regulation of water and electrolyte balance

2-Regulation of acid-base balance

3)Regulation of ABP:

a-Short term: RAAS

B-long term: via excretion of variable amount of NA & water to keep plasma volume constant .

4-Excretion of metabolic waste products e.g. urea, uric acid, creatinine , metabolites of hormone.

5-Excretion of foreign chemicals e.g Drugs

6- Endocrinal function : Kidney secretes :

i. Erythropoirtin
ii. 1,25 Dihydroxy cholecalciferol(Activevitamin D)
iii. Renin

7-Paracrinal Function : Kidney secretes:

I. Prostaglandins

8-Gluconeogenisis during prolonged fasting

PHYSIOLOGICAL ANATOMY OF KIDNEY

Weight: each adult kidney weighs 150 gram.

Size : Clinched fist < 12 cm length <8 cm width

The renal mass is divided into 2 major regions:

A-An outer cortex : granular and deeper in color

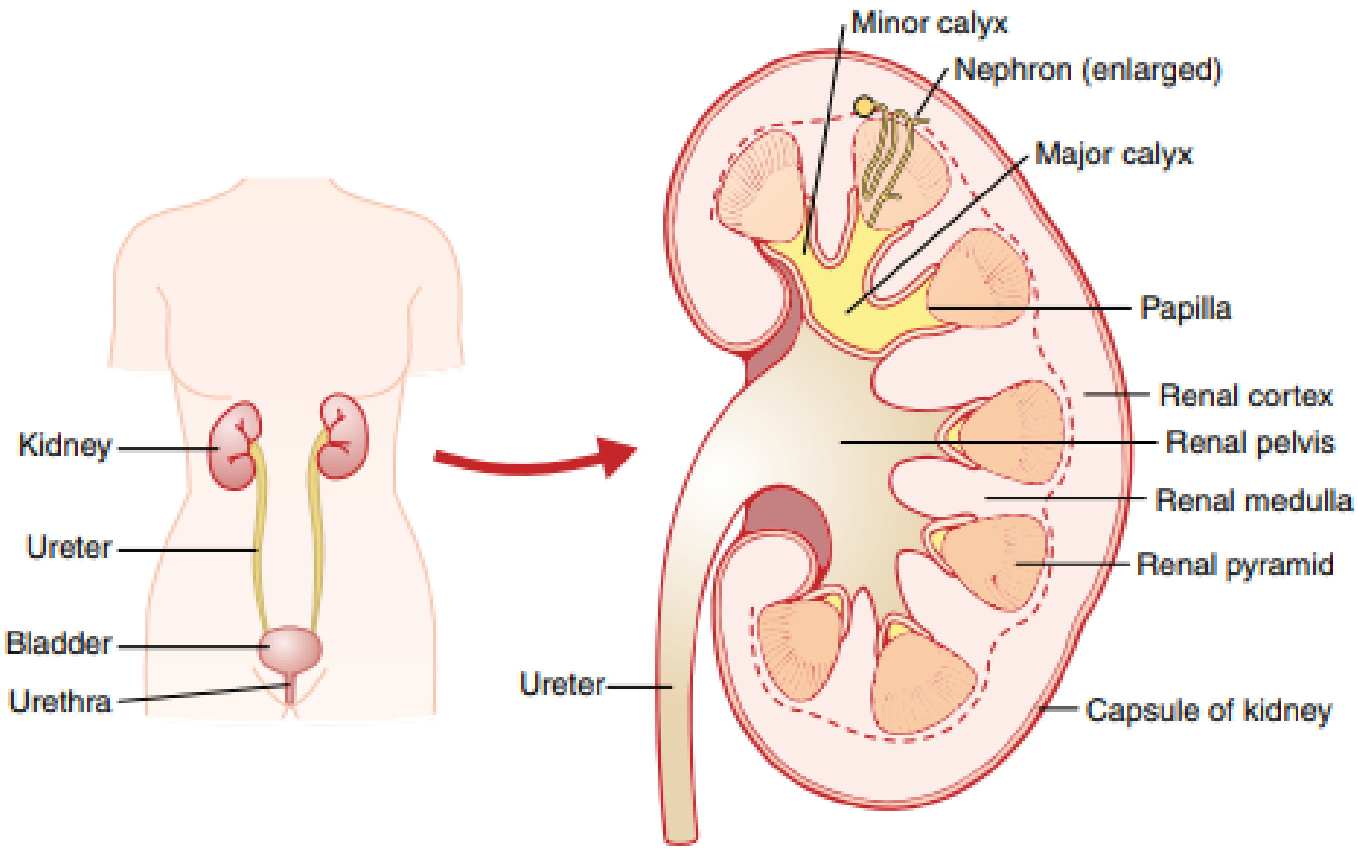
B-An inner medulla : striated and paler in color

The medulla is divided into Pyramids.

Each pyramid tapers to form a renal papilla.

Each papilla projects into the pelvic space via minor calyx

The minor calyces converge into 2 or 3 major calyces, which converge to form the pelvic of the ureter.


Kidney
Ureter
Bladder
Urethra
Minor calyx
Nephron (enlarged)
Major calyx
Papilla
Renal cortex
Renal pelvis
Renal medulla
Renal pyramid
Ureter
Capsule of kidney

Microscopic anatomy

Each human kidney contains 1.3 million nephron.

Nephron is the functional unit of the kidney.

Each nephron acts as a separate entity & is composed of :

a)Glomerulus; a tuft of capillaries which lies within the dilated blind end of renal tubule(Bowman's capsule).

These capillaries lie between afferent arteriole and a smaller efferent arteriole.

Glomerulus is a high pressure capillary bed 60 mmHg.

B)Renal tubule: is divided into:

1)Proximal convoluted tubule: PCT

15 mm long that lies in the cortex.

It is made up of single layer of cells.

2) Loop of henle : U shape, that dips in the renal medulla.

It is composed of :

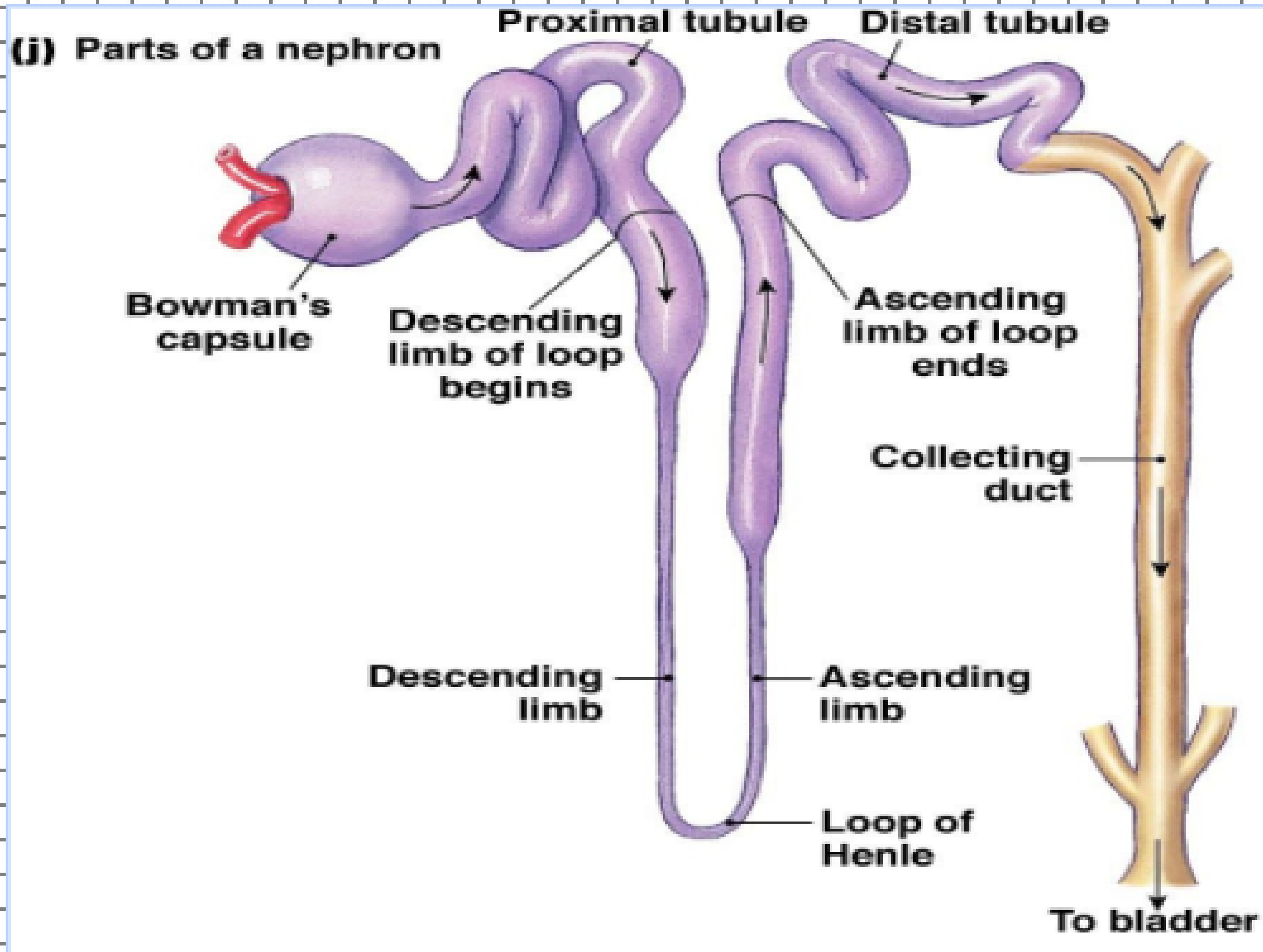
Thin segment : descending limb & lower ½ of ascending limb (lined by flat epithelium)

Thick segment : rest of ascending limb . It is lined by cuboidal cells

3)Distal convoluted tubule : 5 mm long that lies in the cortex.

4) Collecting duct :

20 mm that passes through cortex & medulla


(j) Parts of a nephron
Proximal tubule
Distal tubule
Bowman's capsule
Descending limb of loop begins
Ascending limb of loop ends
Collecting duct
Descending limb
Ascending limb
Loop of Henle
To bladder

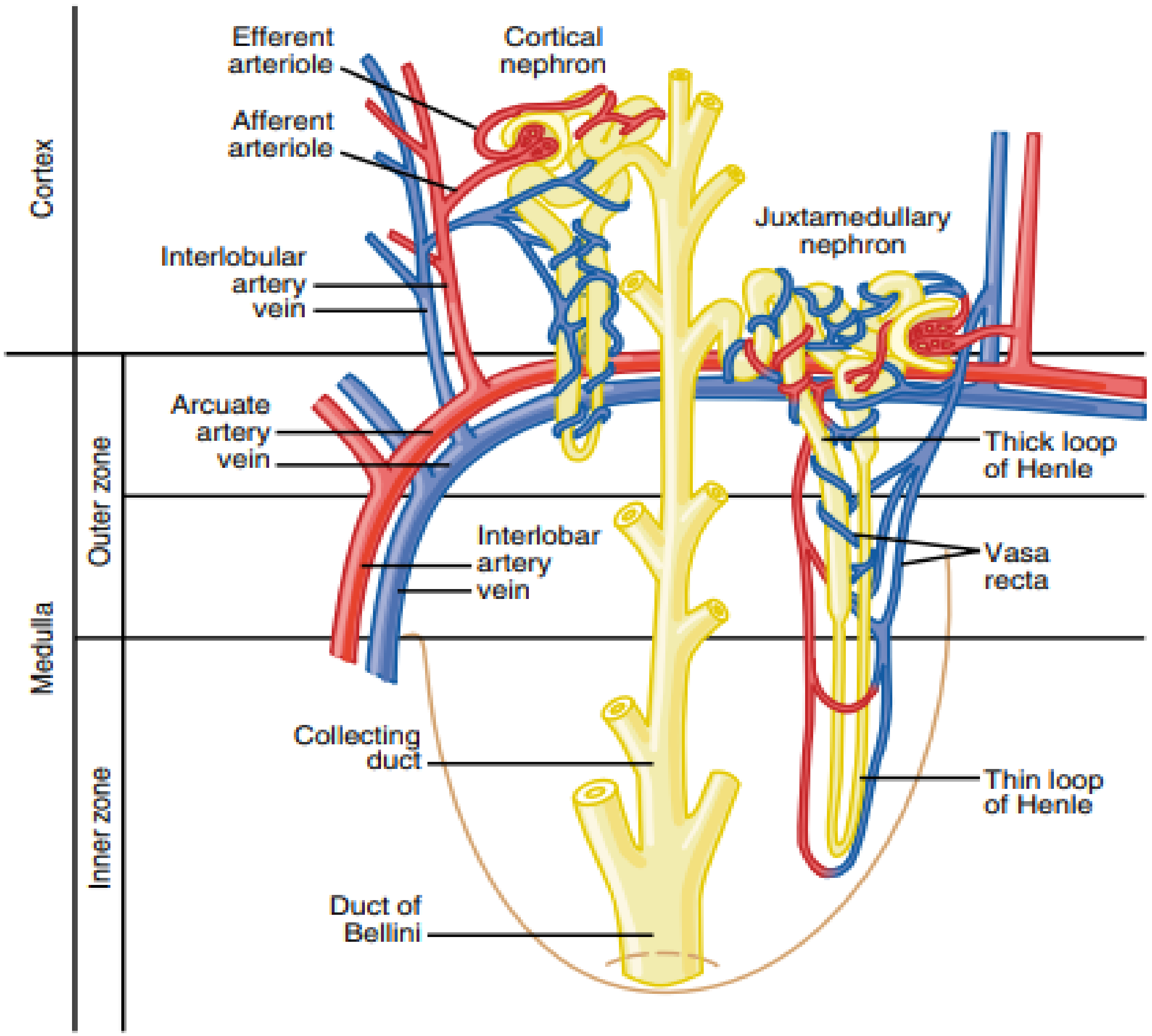
Collecting Ducts (CD)

- Each 8 DCTs unite together forming cortical CD that pass to medulla to form medullary CD that unite together forming minor calyces, then major calyces, then renal pelvis and finally the ureter. It is lined by:

Principal cells (P-cells)	**Intercalated cells (I-cells)**
Predominate with few organells	Less in number with more **m**itochondria, **m**icrovilli & cytoplasmic vesicles.
Na^+ **r**eabsorption (controlled by **A**ldosterone) **Water** **r**eabsorption (controlled by **A**DH)	Involved in **H^+ secretion & HCO_3^- transport** (also, found in DCT).

There are 2 types of the nephrons:

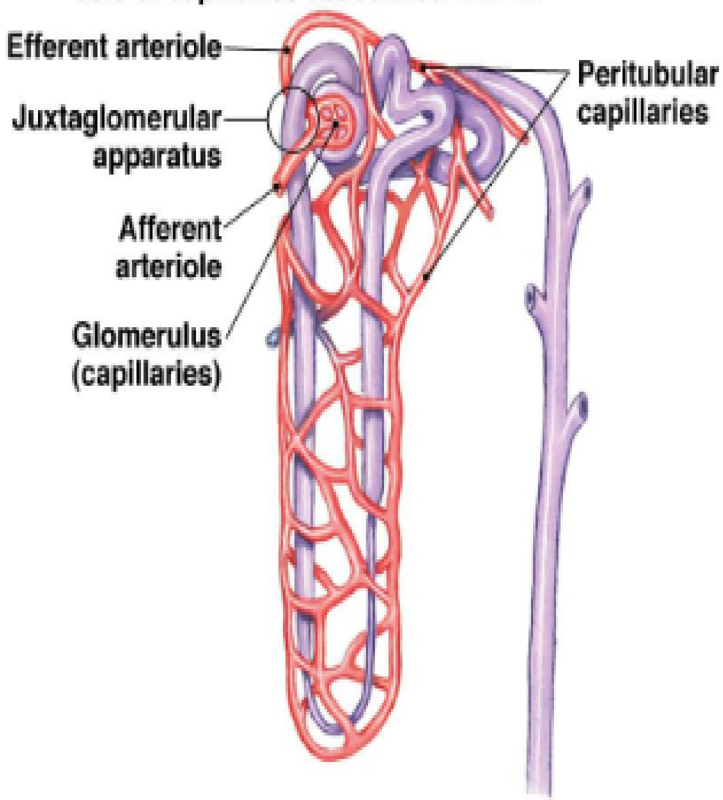
S. No.	Cortical Nephrons (70-80%)	Juxtamedullary Nephrons (20-30%)
1	Found in cortex	Found at the function of renal cortex and medulla.
2	Have relatively short loop of Henle	Have longer loop of Henle and Vasa recta.
3	Under normal water conditions, this nephron deals with the control of blood volume.	In case of deficient water supply, increased water retention occurs through this nephron



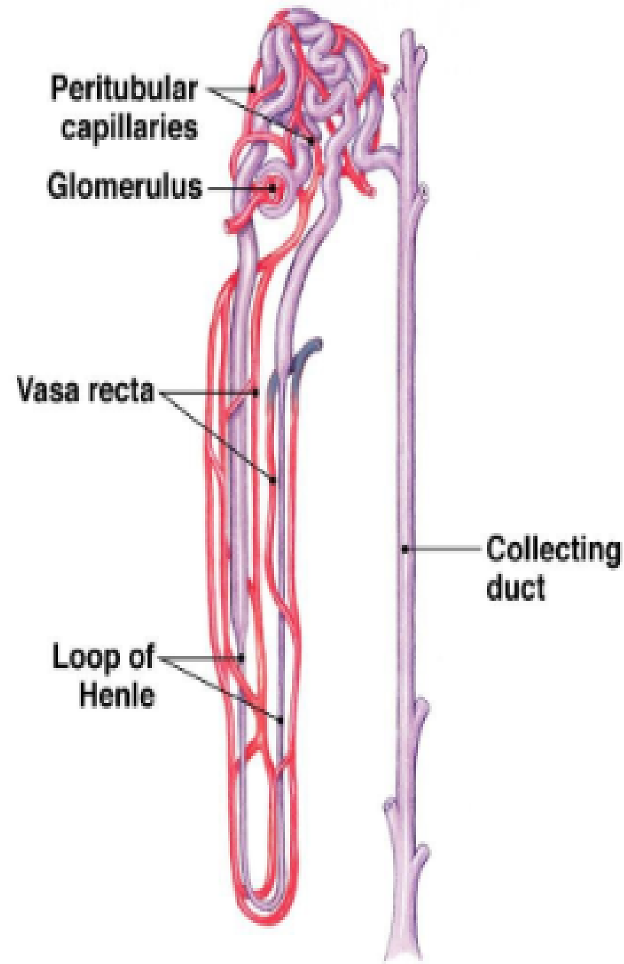
Efferent arteriole
Cortical nephron
Afferent arteriole
Cortex
Interlobular artery
vein
Juxtamedullary nephron
Arcuate artery
vein
Outer zone
Thick loop of Henle
Interlobar artery
vein
Vasa recta
Medulla
Collecting duct
Inner zone
Thin loop of Henle
Duct of Bellini

Cortical nephrons

(g) Each nephron has two arterioles and two sets of capillaries associated with it.



(h) Juxtamedullary nephron with vasa recta



The two types of nephrons and their features

Feature	Juxtamedullary nephron	Cortical nephron
Percentage	15%	85%
Renal capsule situation	Inner cortex is near medulla	Outer cortex is near periphery
Tubule blood supply	Vasa recta	Peritubular capillaries
Function	Concentrates urine (mainly), and also forms urine	Forms urine
Loop of Henle	Long	short
	Hairpin bend penetrates up to the tip of papilla	Hairpin bend penetrates only to outer zone of medulla

juxtaglomerular apparatus

Specialized tubular & vascular cells at area of contact between the distal convoluted tubule and the afferent and efferent arterioles at the vascular pole , where they enter & leave the glomerulus.

It consists of :

1)Macula densa : They are modified tubular cells in the first part of DCT in close proximity to juxta-glomerular cells.

Macula densa monitor the composition of tubular fluid (function as chemoreceptors) that is stimulated by a decrease of NaCl load in DCT

2) juxta glomerular cells :

Granular cells

Located in media mainly of afferent arteriole .

Secrete renin

Act as baroreceptors stimulated by decreases renal perfusion or by hypovolemia.

3)Lacis cells :

Agranular

Located between afferent and efferent arterioles

Store renin.

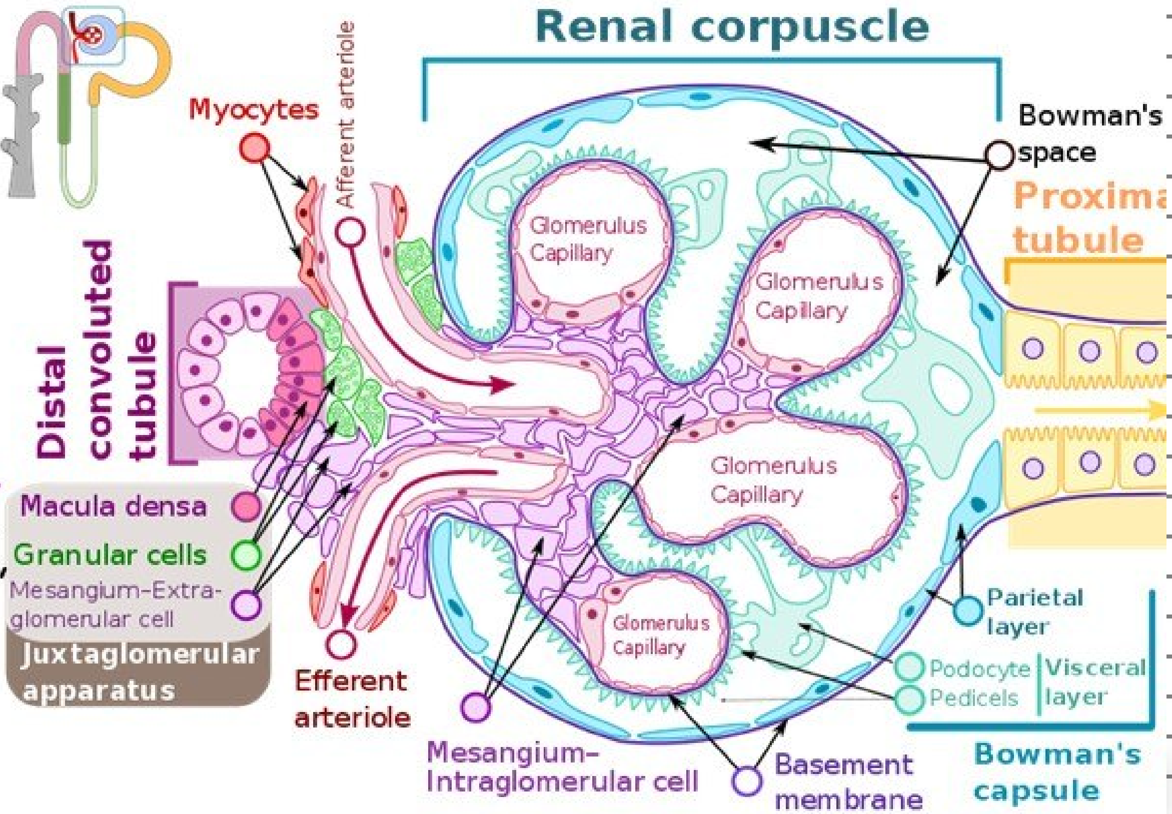
Juxtaglomerular Apparatus (JGA)

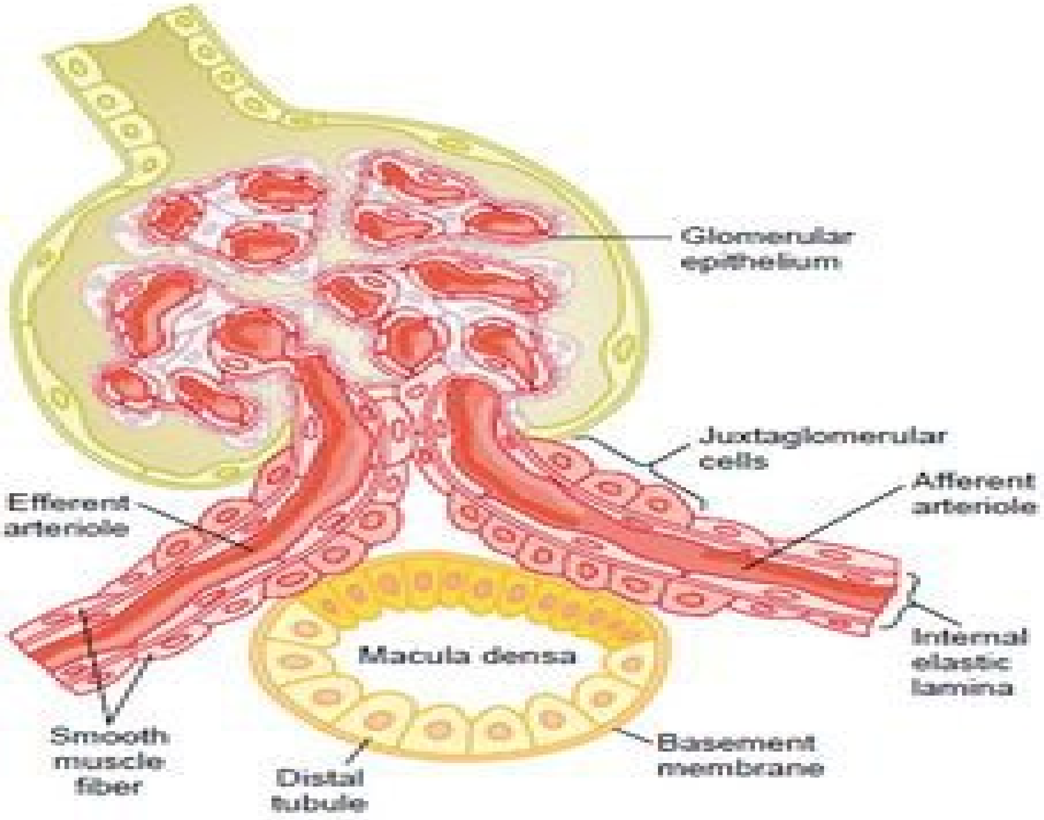
The JGA (or complex) is a structure in the kidney and regulates the function of each nephron. The JGA is named because it is next to (juxta) the glomerulus

The JGA consists of three types of cells: 1- macula densa, a part of the distal convoluted tubule of the same nephron. 2- juxtaglomerular cells (also known as granular cells) which secrete renin (R). 3- extraglomerular mesangial cells

Clinical significance

Excess secretion of R by the JGA cells can lead to HT and an increase in blood volume. One cause of this can be increased R production due to narrowing of the RA, or a tumour of JGA cells. These will lead to secondary hyperaldosteronism, which will cause HT, high blood Na, low blood K, and metabolic alkalosis





Glomerular epithelium
Juxtaglomerular cells
Afferent arteriole
Efferent arteriole
Internal elastic lamina
Macula densa
Smooth muscle fiber
Distal tubule
Basement membrane

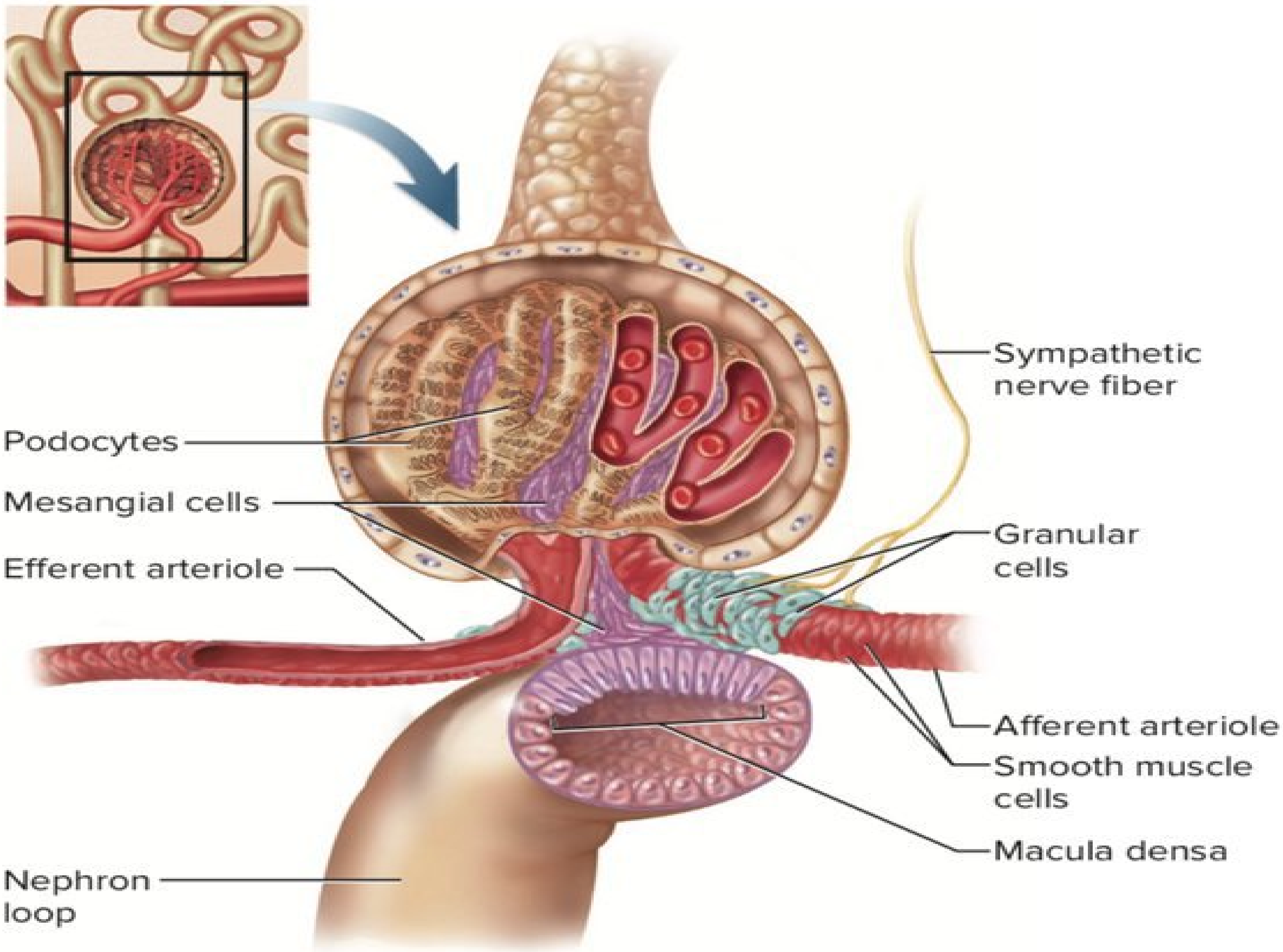
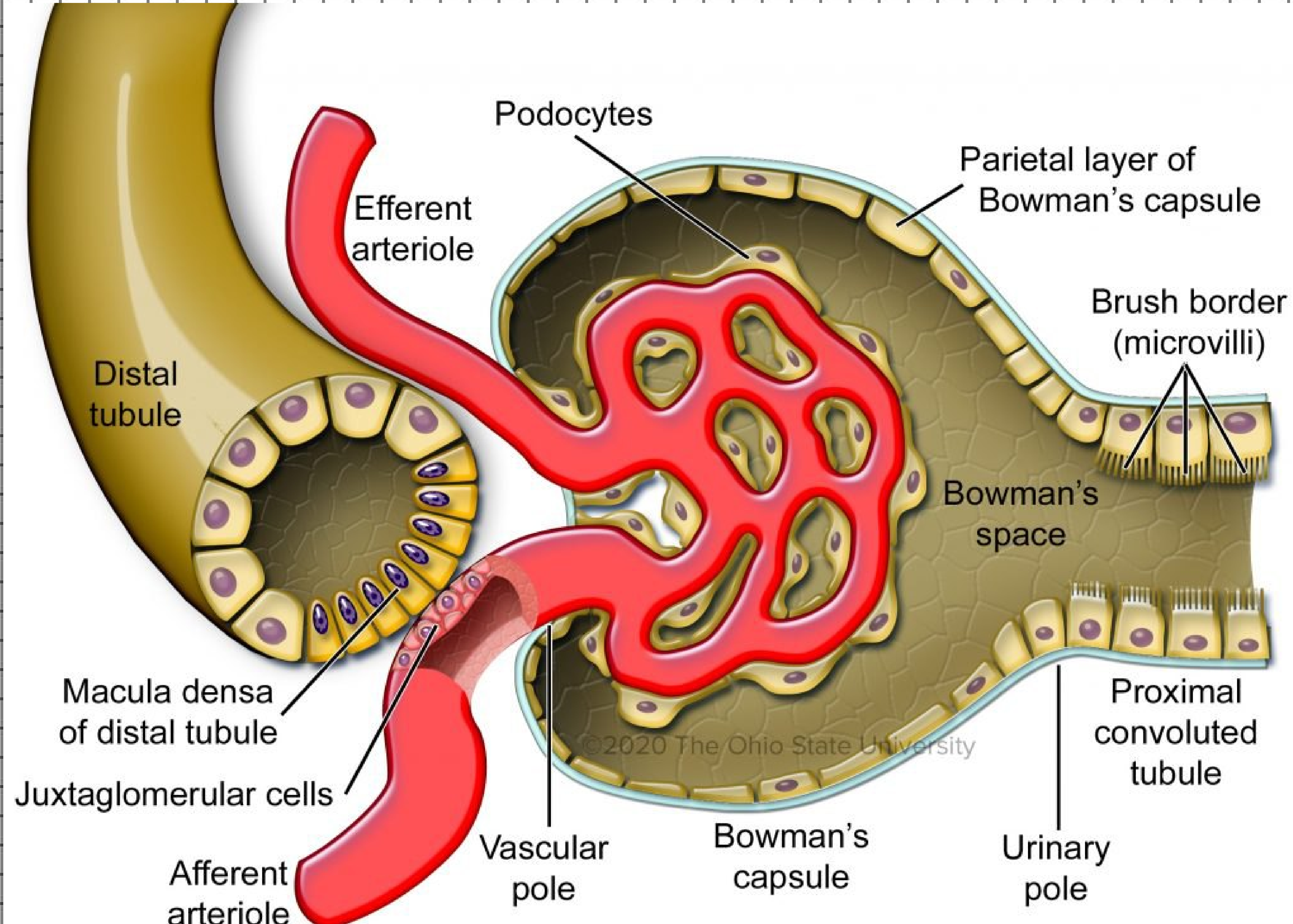


FIGURE 23.13 **The Juxtaglomerular Apparatus.**


Podocytes
Parietal layer of Bowman's capsule
Efferent arteriole
Brush border (microvilli)
Distal tubule
Bowman's space
Macula densa of distal tubule
Juxtaglomerular cells
Proximal convoluted tubule
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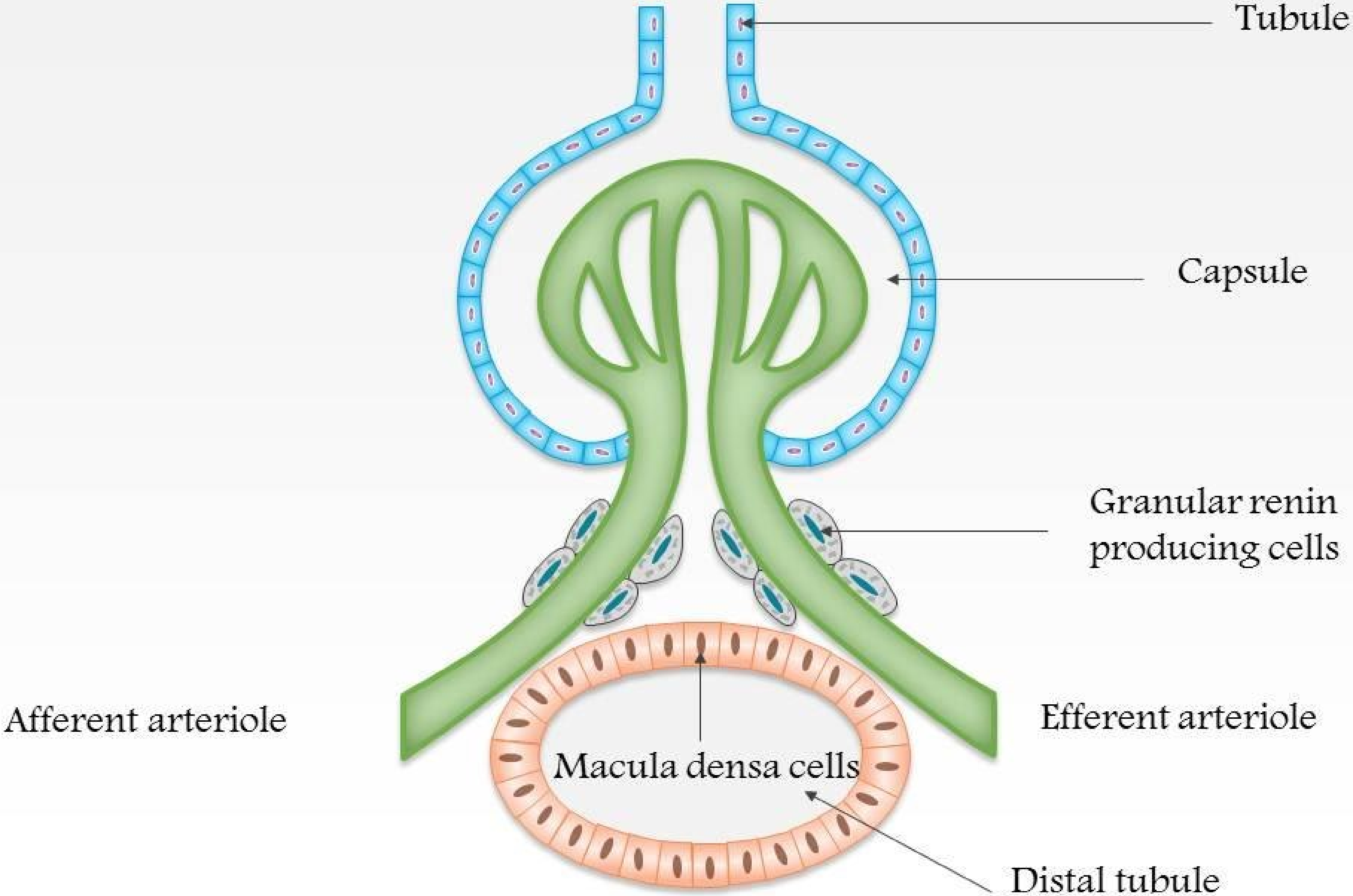
Afferent arteriole
Vascular pole
Bowman's capsule
Urinary pole

Juxtaglomerular apparatus



TUBULOGLOMERULAR FEEDBACK

- special feedback mechanism
- depend on special anatomical arrangements of the juxtaglomerular complex
- autoregulates renal blood flow and GFR in parallel In many circumstances
- However, instances
- occur when GFR is autoregulated at the expense of changes in renal blood flow.
- The tubuloglomerular feedback mechanism has two components that act together to control GFR:
  - (1) an afferent arteriolar feedback mechanism;
  - (2) an efferent arteriolar feedback mechanism.
- The juxtaglomerular complex:
  - Macula densa cells in the initial portion of the distal tubule
  - juxtaglomerular cells in the walls of the afferent and efferent arterioles

Decreased Macula Densa Sodium Chloride Causes Dilation of Afferent Arterioles and Increased Renin Release.

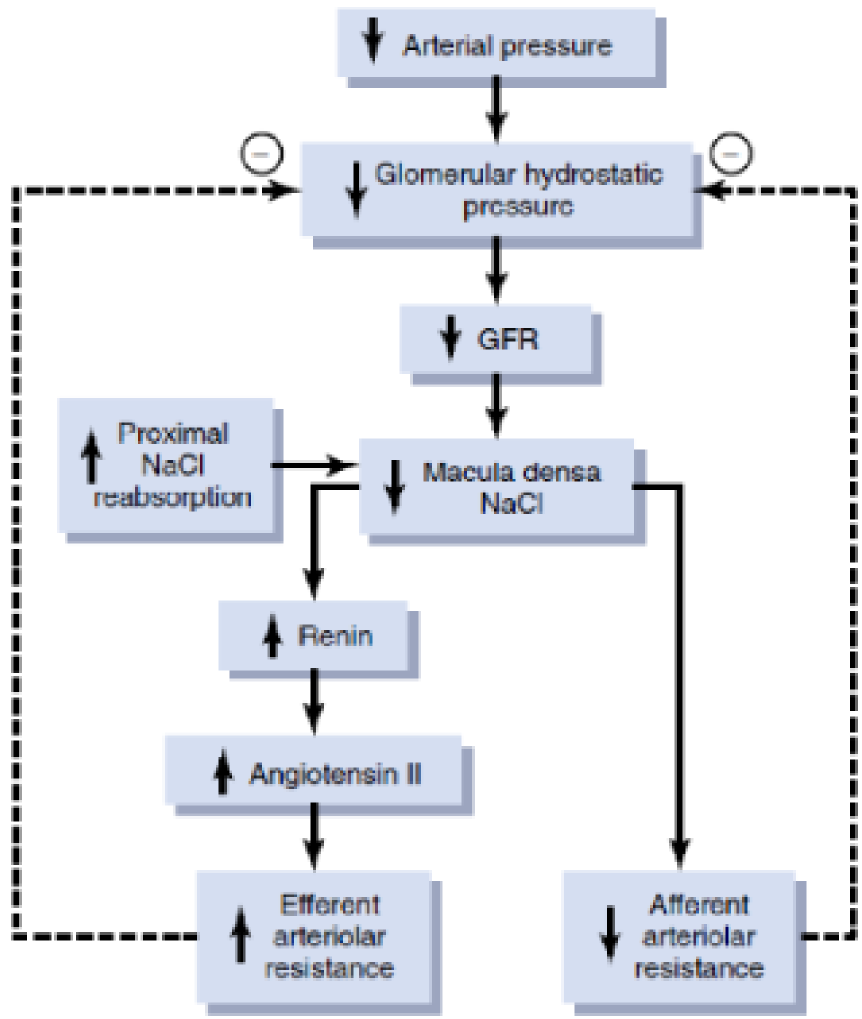
The macula densa cells sense changes in sodium chloride delivery to the distal tubule.

initiates a signal from the macula densa that has two effects:

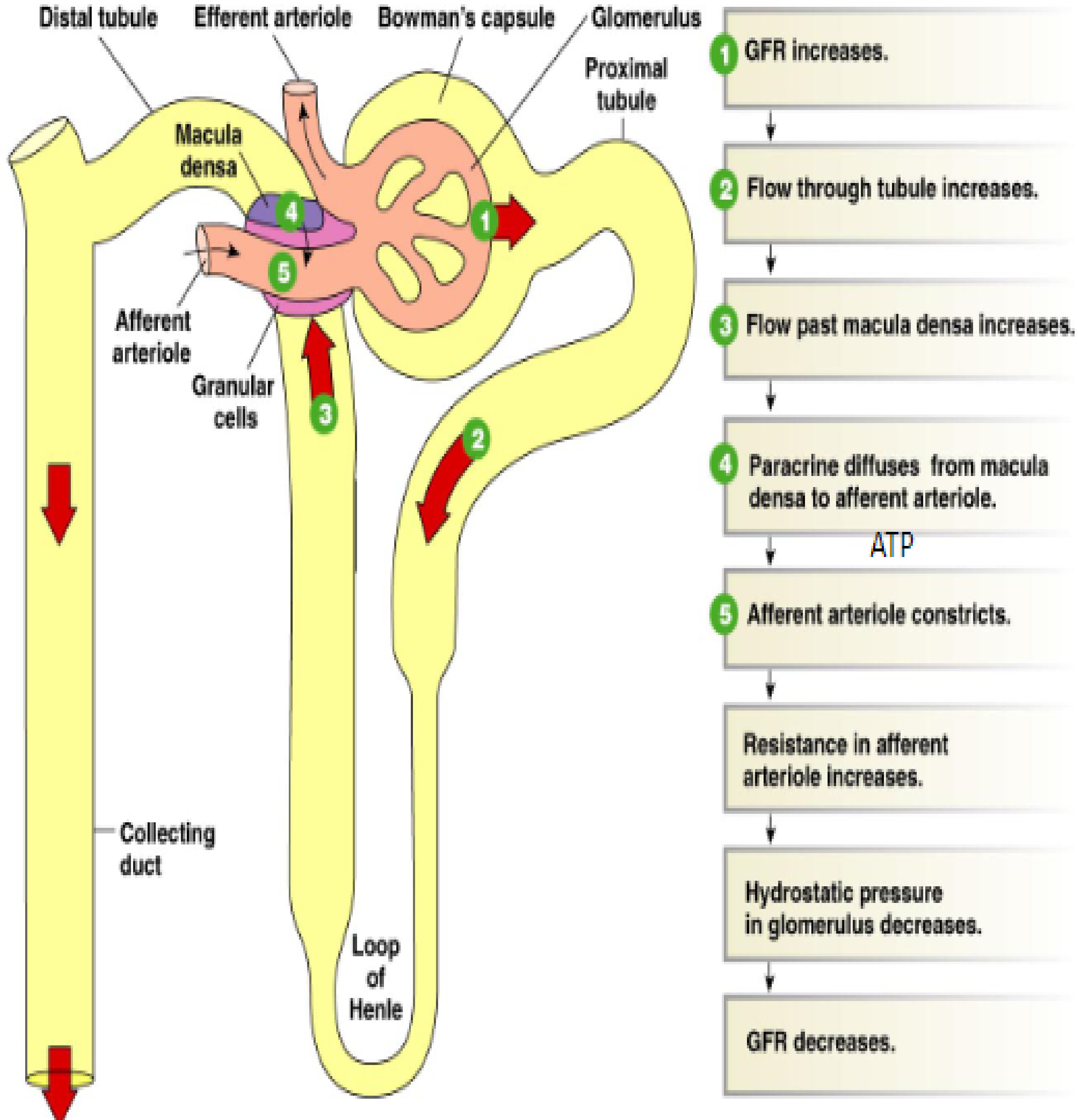
(1) it decreases resistance to blood flow in the afferent arterioles, which raises glomerular hydrostatic pressure and helps return GFR toward normal;

(2) it increases renin release from the juxtaglomerular cells of the afferent and efferent arterioles, which are the major storage sites for renin.

Renin increase the formation of angiotensin I an II increasing glomerular hydrostatic pressure and helping return GFR toward normal.


Arterial pressure
Glomerular hydrostatic pressure
GFR
Proximal NaCl reabsorption
Macula densa NaCl
Renin
Angiotensin II
Efferent arteriolar resistance
Afferent arteriolar resistance

Tubuloglomerular feedback helps GFR autoregulation.



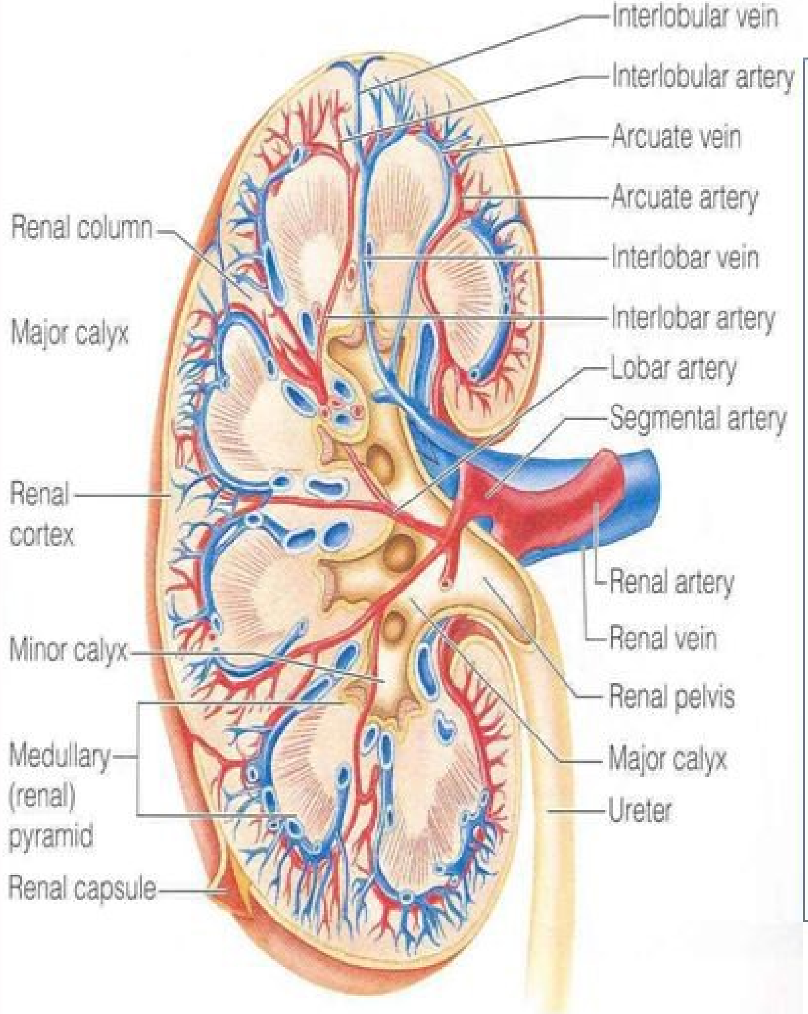
Renal Blood flow : RBF

Kidneys receive 20-25% of COP , 1.2-1.3 L/min

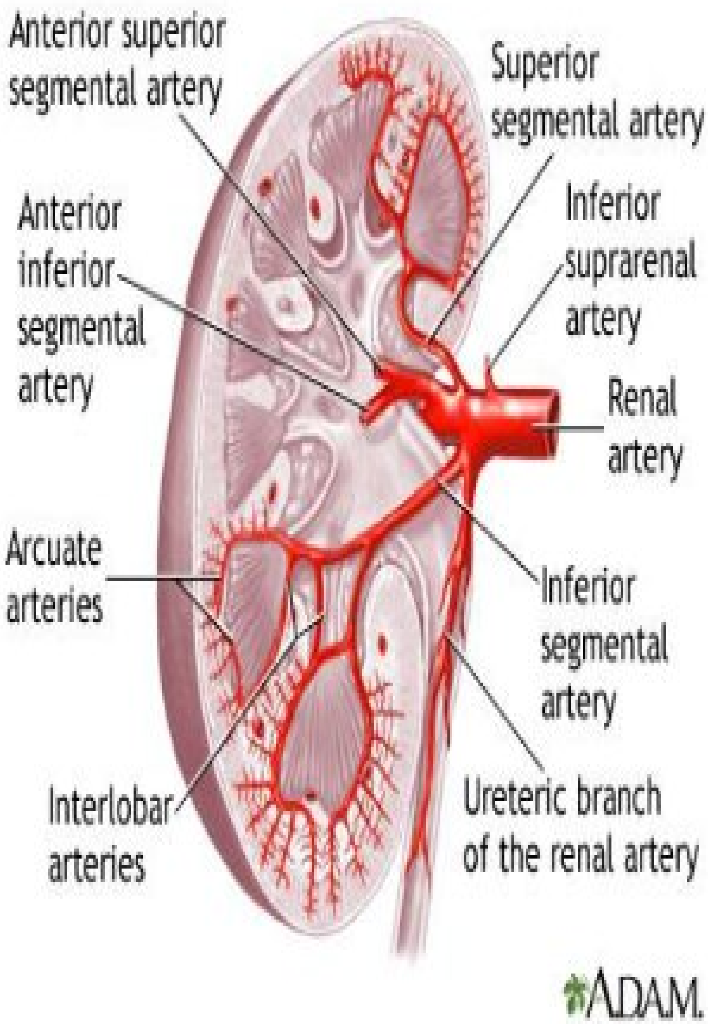
Renal vascular arrangment:

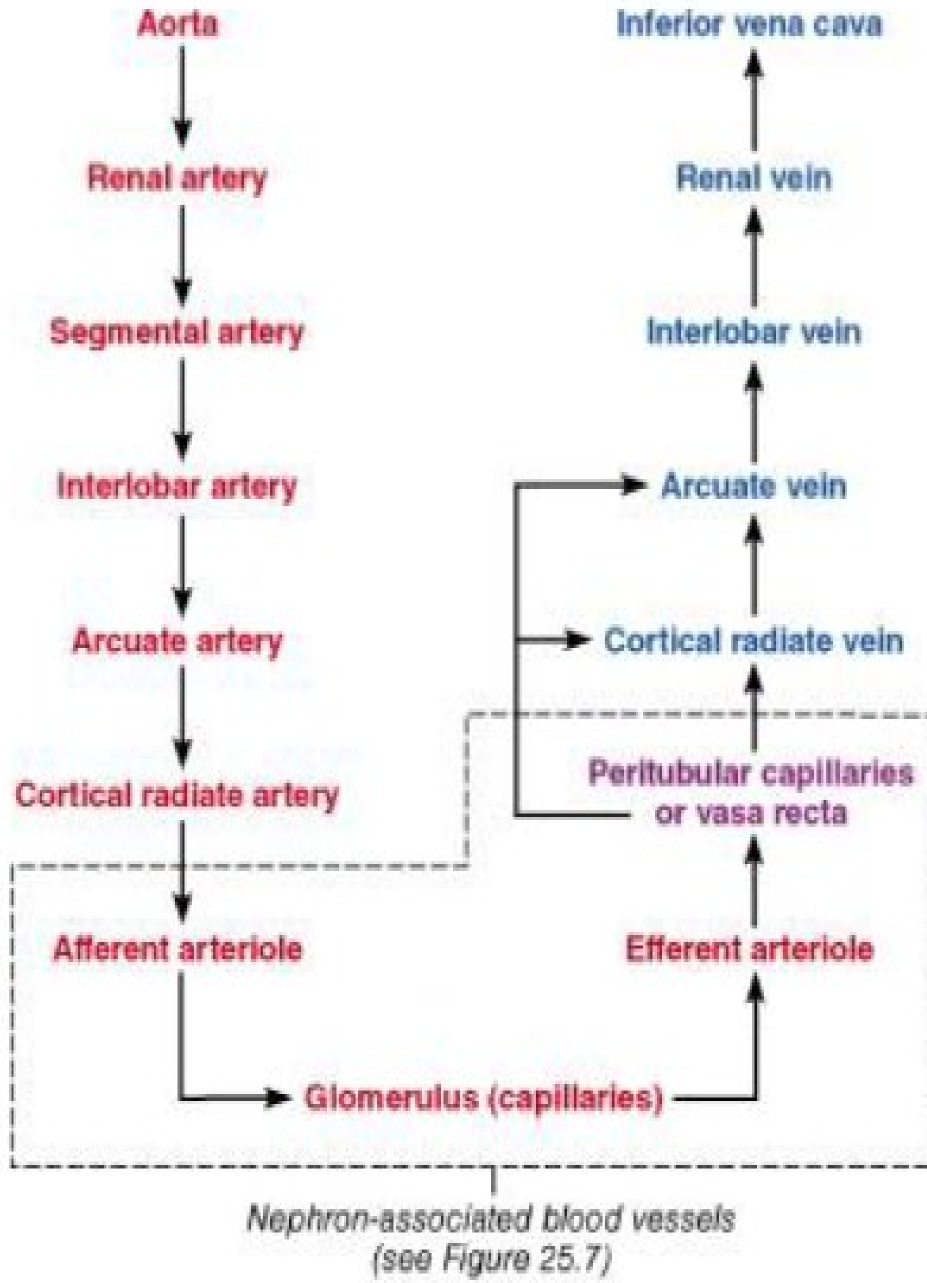
Blood Supply

- Abdominal aorta
  ↓
- Renal artery
  ↓
- Segmental arteries
  ↓
- lobar arteries
  ↓
- Interlobar arteries
  ↓
- Arcuate arteries
  ↓
- Interlobular arteries
  ↓
- **afferent glomerular arterioles**



- Inferior vena cava
  ↑
- Renal vein
  ↑
- Interlobar veins
  ↑
- Arcuate veins
  ↑
- Interlobular veins





(b) Path of blood flow through renal blood vessels

Arterial System

Renal Artery

↓

Segmental Artery

↓

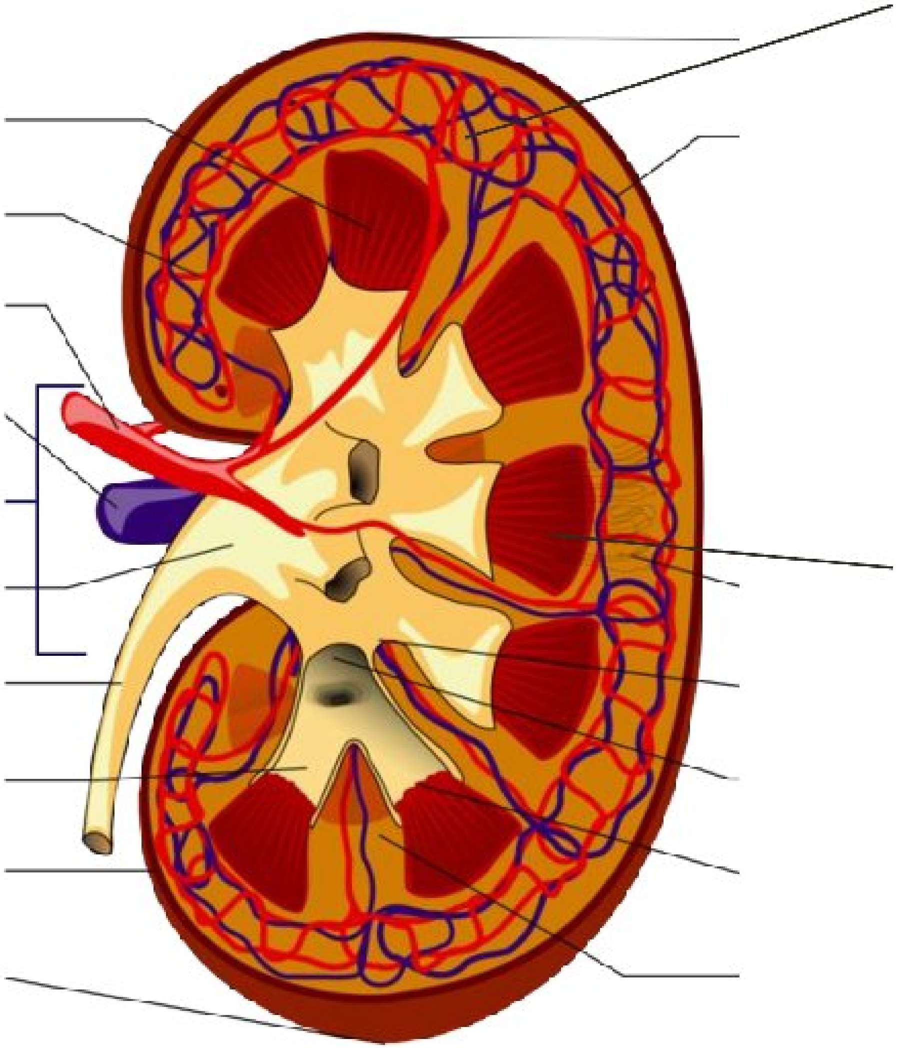
Interlobar Artery

↓

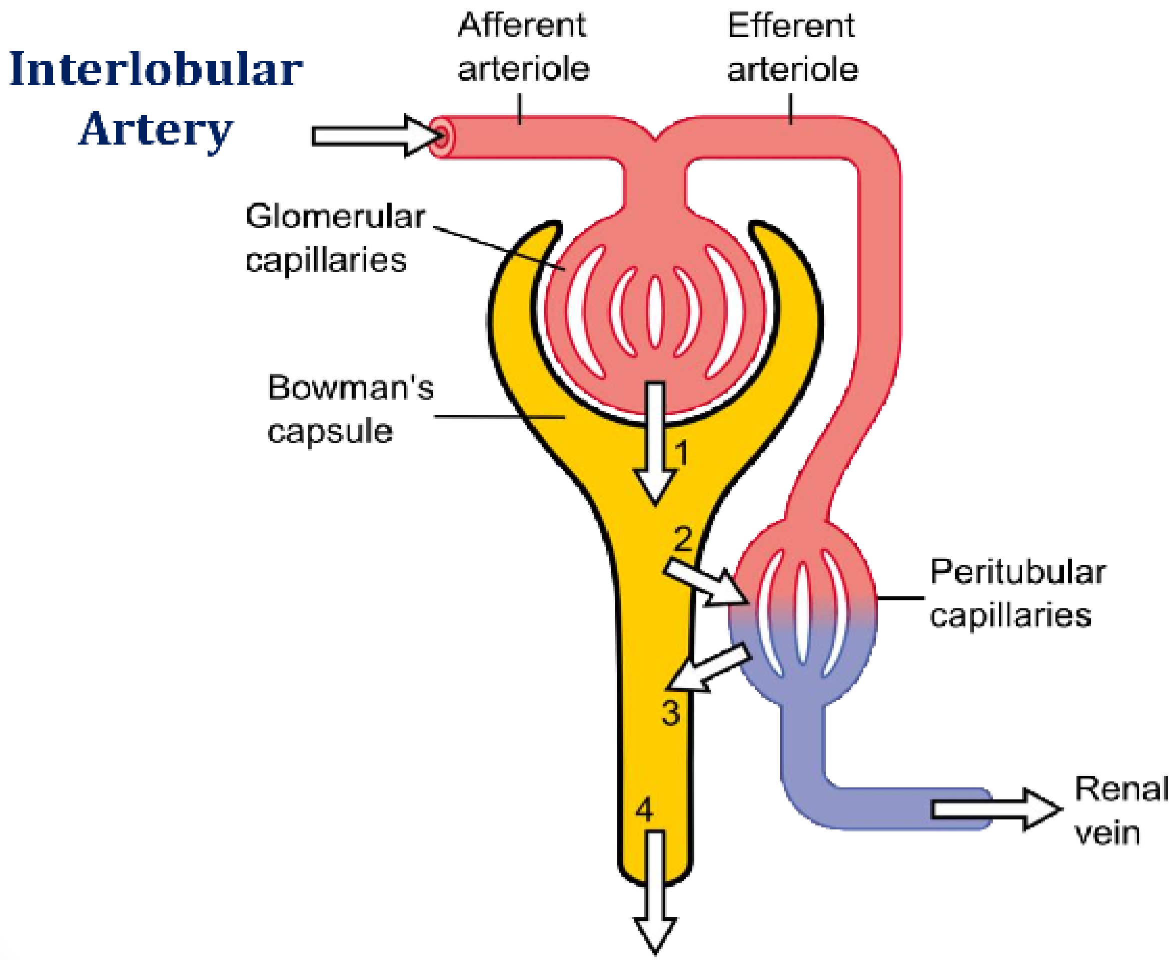
Arcuate Artery

↓

Glomerulus ← **Interlobular Artery**



Glomerular Blood Flow



There are 2 capillary bed related to each nephron:

Pritubular	Glomerular
Receive blood	Receive blood
Low pressure 13	High pressure
Represents venous end of	Represents arterial end of
It allows fluid reabsorption.	It allows fluid filtration

The pressure in the glomerular capillary is high due to :

1-Renal artery is a direct branch of the abdominal aorta

2-Afferent arteriole is a short straight branch of interlobular artery

3-Efferent arteriole has a high resistance than the afferent

Which changes tends to increase peritubular capillary fluid reabsorption ?

A. Increase blood pressure
B. Decreased filtration fraction
C. Increased efferent arteriolar resistance
D. Decreased angiotensin II
E. Increases renal blood flow

C

Regional blood flow :

Renal cortex receives most of the renal blood flow to filtrate large volumes of blood through the glomeruli.

Renal medullary blood flow accounts only for 1-2% of the renal blood flow

A patient with chronic kidney disease is found to be hypotensive in the ICU . Which portion of the nephron is most affected by this acute insult?

Medulla –has lower PO2

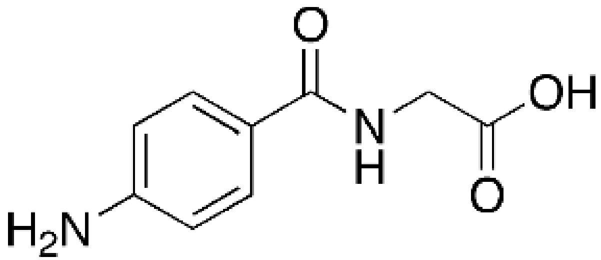
Medulla has capillary loops surrounding the loops of Henle Known as vasa recta.

Slow flow through these vessels keeps the PO2 of medulla lower than in the cortex – more susceptible to ischemic damage.

Renal Plasma Flow (RPF)

- Use **para-aminohippuric acid (PAH)** to estimate RPF
- PAH is filtered and secreted
- 100% of PAH that enters kidney leaves blood in urine
- Clearance PAH (l/min) = Plasma to kidney (l/min)

$$C_{PAH} = \frac{U_{PAH} * V}{P_{PAH}} = RPF$$



PAH

*PAH clearance underestimates RPF by 10%
Not all renal plasma/blood to glomeruli

Boards&Beyond STUDY SMARTER

Plasma versus Blood

- Blood = Plasma + cells/proteins
- Renal Blood Flow > Renal Plasma Flow
- Separate calculations RBF vs. RPF

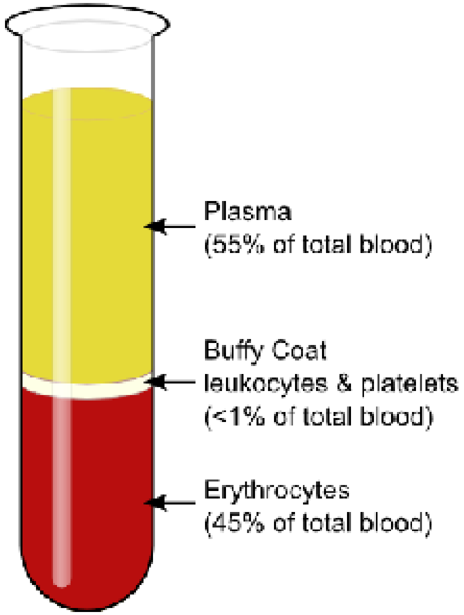


Image courtesy of KnuteKnudsen

Renal Blood Flow (RBF)

- RBF determined from RPF
- Blood = Plasma + Cells/Proteins
- Cells/Proteins (%) ≈ Hct (%)

$$RPF = RBF\ (1\text{-}Hct)$$

RBF = 10cc/min
40% of cells (Hct)
60% RBF is plasma
RPF = 10 (1- 0.4) = 10 (0.6)
= 6cc/min

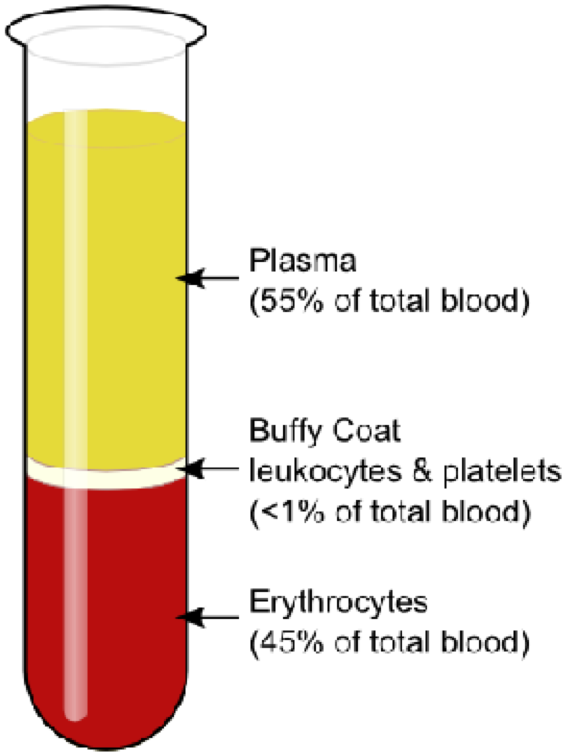


Image courtesy of KnuteKnudsen

Renal Blood Flow (RBF)

- RBF determined from RPF
- Blood = Plasma + Cells/Proteins
- Cells/Proteins (%) ≈ Hct (%)

$$RPF = RBF\,(1\text{-}Hct)$$

$$RBF = \frac{RPF}{1 - Hct}$$

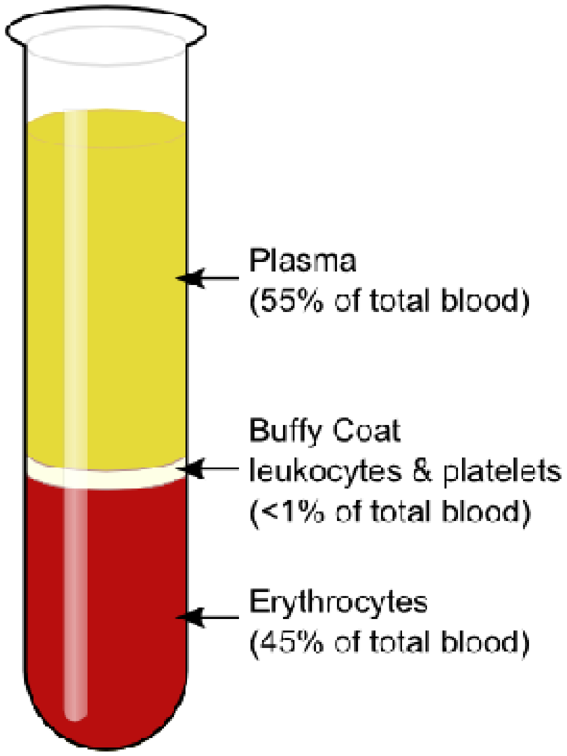


Image courtesy of KnuteKnudsen

Renal Blood Flow (RBF)

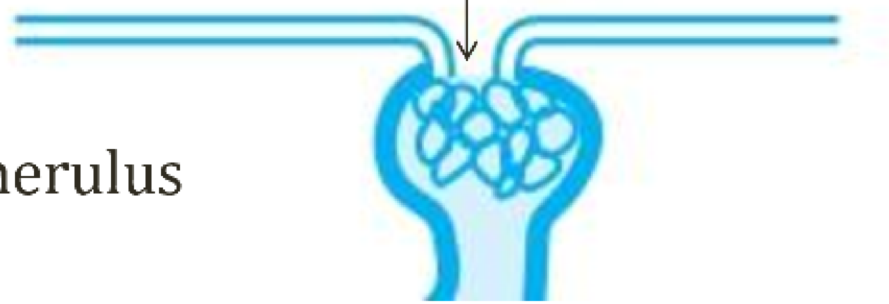
- RPF = 1 liter/min
- Hct = 40%

$$RBF = \frac{1}{1 - Hct} = \frac{1}{0.6} = 1.6 \text{ l/min}$$

Renal Function Measurements

GFR
Fluid across Glomerulus
Inulin/Creatinine

RPF
Fluid into Glomerulus
PAH



Urine Flow
Fluid out of kidney

Auto regulation of RBF

at high pressure

muscles of arteries are intrinsic myogenic in nature >>vasoconstriction >>> decrease RBF

at low pressure

tubuloglomerular feed back

Tubuloglomerular feedback

Myogenic autoregulation of RBF&GFR

Ability of individual blood vessels to resist stretching during ↑ arterial pressure (myogenic mechanism)

↑Wall tension→ allow ↑ movement ofCa into cells→ vascular smooth muscles contraction (small arterioles) → prevent overdistension of vessels, helps prevent excessive increases of RBF and GFR when BP increases.

Formation of urine

Urine is formed in three main steps:

glomerular filtration

reabsorption

and secretion.

Excretion refers to what finally comes out in urine .

It represents the sum of 3 processes

Urinary excretion rate = Filtration rate −reabsorption rate + secretion rate

Glomerular filtration

Glomerular filtrate:

It is a protein free ultra filtrate.

1-Compostion:

Plasma minus colloid (Plasma protein)

Volume:

Normal GFR : In average man: 125 ml/min

In women : 10 % less

More than 99% of GFR is reabsorbed

GFR decrease with age

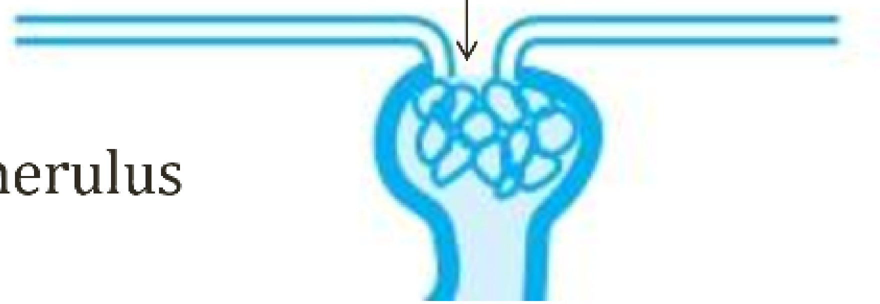
Filtration fraction

It is ratio of GFR to renal plasma flow.

Normal value : 16% to 20%

Renal Function Measurements

GFR
Fluid across Glomerulus



RPF
Fluid into Glomerulus

Urine Flow
Fluid out of kidney

RPF = 5L/min
GFR = 2L/min
Filtration Fraction=2/5=40%

Glomerular membrane

It is formed of 3 layers

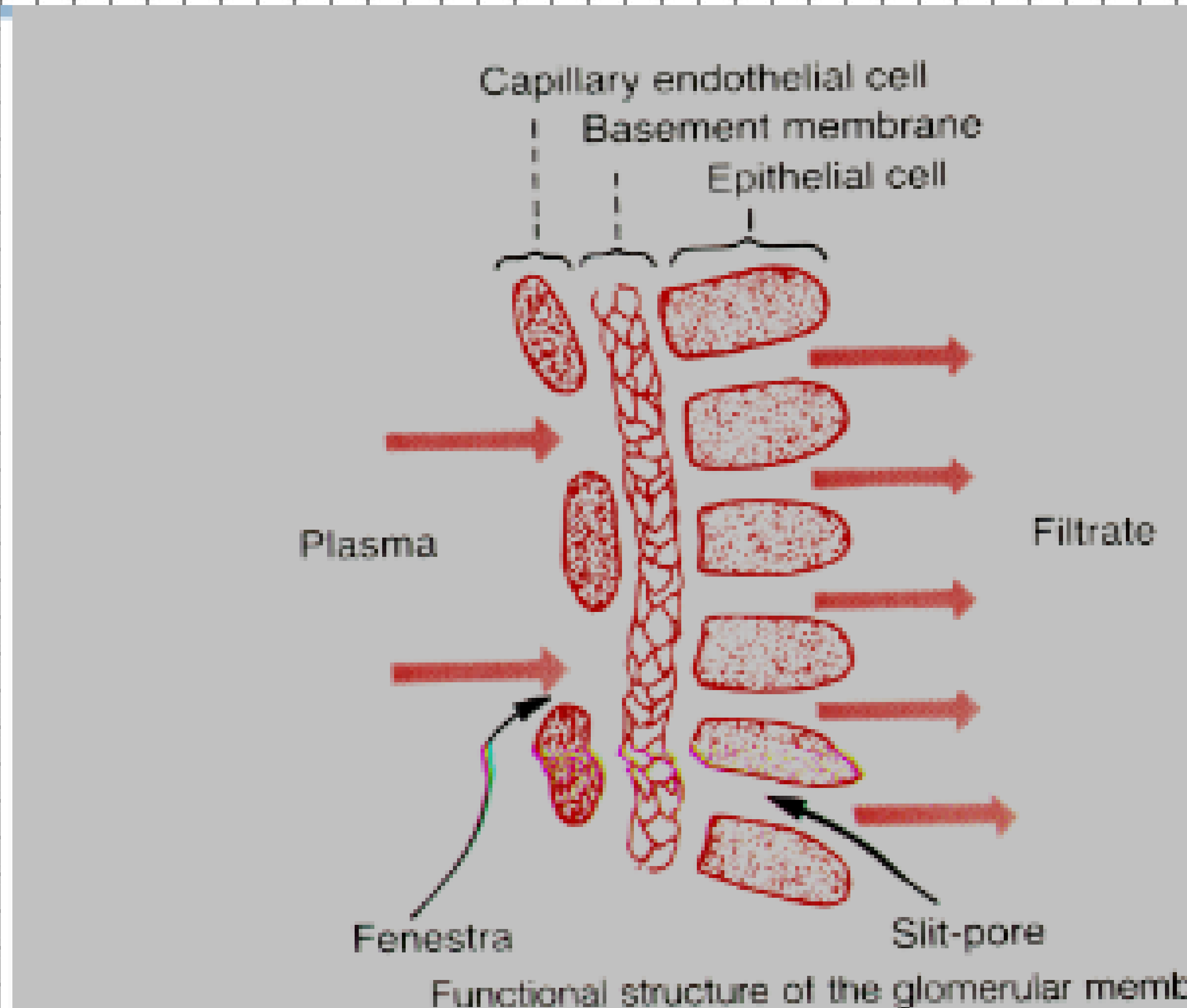
1.Capillary endothelium:

It has small hole (70-90nm)

2.Basement membrane

It is meshwork of collagen and proteoglycan that has large spaces , the proteoglycan carry strong negative charges which prevent the filtration of plasma proteins

3.Podocytes


Capillary endothelial cell
Basement membrane
Epithelial cell
Plasma
Filtrate
Fenestra
Slit-pore
Functional structure of the glomerular memb

Mesangial cells

They are stellate cells located between the basement membrane and the endothelium at bifurcation of the capillaries

They are contractile cells.

Functions of mesangial cells :

1-Regulate GFR (when contract will reduce filtration area)

2-Take up immune complexes

Permeability of glomerular membrane

-depends on:

size of molecules: filtration is inversely proportional to diameter between 4-8 nm

Less than 4 nm, the molecules are freely filtered

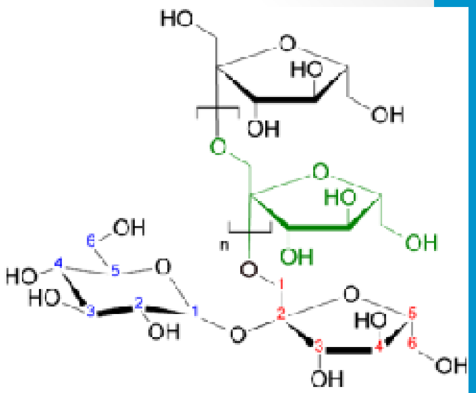
More than 8 nm , the molecules are not filtered

charges of molecule:

Negatively charged molecules e.galbumin (7 nm) is filtered less easily than positively charged molecules of equal size.

Only .2% of albumin plasma is filtered

Determining GFR



- **Inulin clearance** used to determine GFR
- Inulin neither secreted or resorbed
- **All inulin filtered goes out**
- Amount blood "cleared" of inulin is amount of blood filtered by glomerulus
- **Clearance of inulin (liters/min) = GFR**

$$C_{inulin} = \frac{U_{inulin} * V}{P_{inulin}} = GFR$$

Measurement of GFR

Inulin clearance :

Inulin is a polymer of fructose .

Inulin has the following characteristics :

1-freely filtered i.e. plasma conc.=filtrate conc.

2-Not reabsorbed or secreted by renal tubules

Amount filtered per min= amount excreted in urine / min.

3-Not metabolized

4-Not stored in the kidney

5-Does not affect filtration rate

6-Its conc. Is easily measured.

Steps

1-A loading dose is intravenously injected followed by sustained infusion to keep arterial plasma level constant

2-After inulin has been equilibrated in body fluids, urine and plasma samples are taken where inulin concentration is measured.

Calculation

/amount filtered/min=Amount excreted/min

So, C in *P in = V *U

C in =V*U in / P in

P in = inulin concentration in plasma (same conc. In filtrate)

U in = inulin conc. In urine.

V = volume of urine per min.

C in = volume filtered /min

Creatinine clearance

Advantage:

Creatinine is an endogenous substance formed from muscle (no extra work is assesd to kidney)

Characteres of creatinine :

1- Freely filtered

2- Not reabsorbed

3-Partially secreted by renal tubules.

Creatinine

- Breakdown product muscle metabolism
- **Closest naturally occurring substance to inulin**
  - Inulin = All filtered goes out, no secretion/resorption
  - Creatinine = All filtered goes out, small amount secretion
- Using Cr instead of inulin:
  - Secreted Cr will be counted as filtered
  - This will slightly overestimate GFR

Creatinine

$$C_x = \frac{U_x * V}{P_x}$$

- **Special formulas** to convert Cr to GFR
  - Cockcroft-Gault formula
  - Modification of Diet in Renal Disease (MDRD) formula
  - Use age, gender, Cr level to estimate GFR

<u>Cockcroft-Gault</u>

CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

P_{Cr}/GFR Relationship

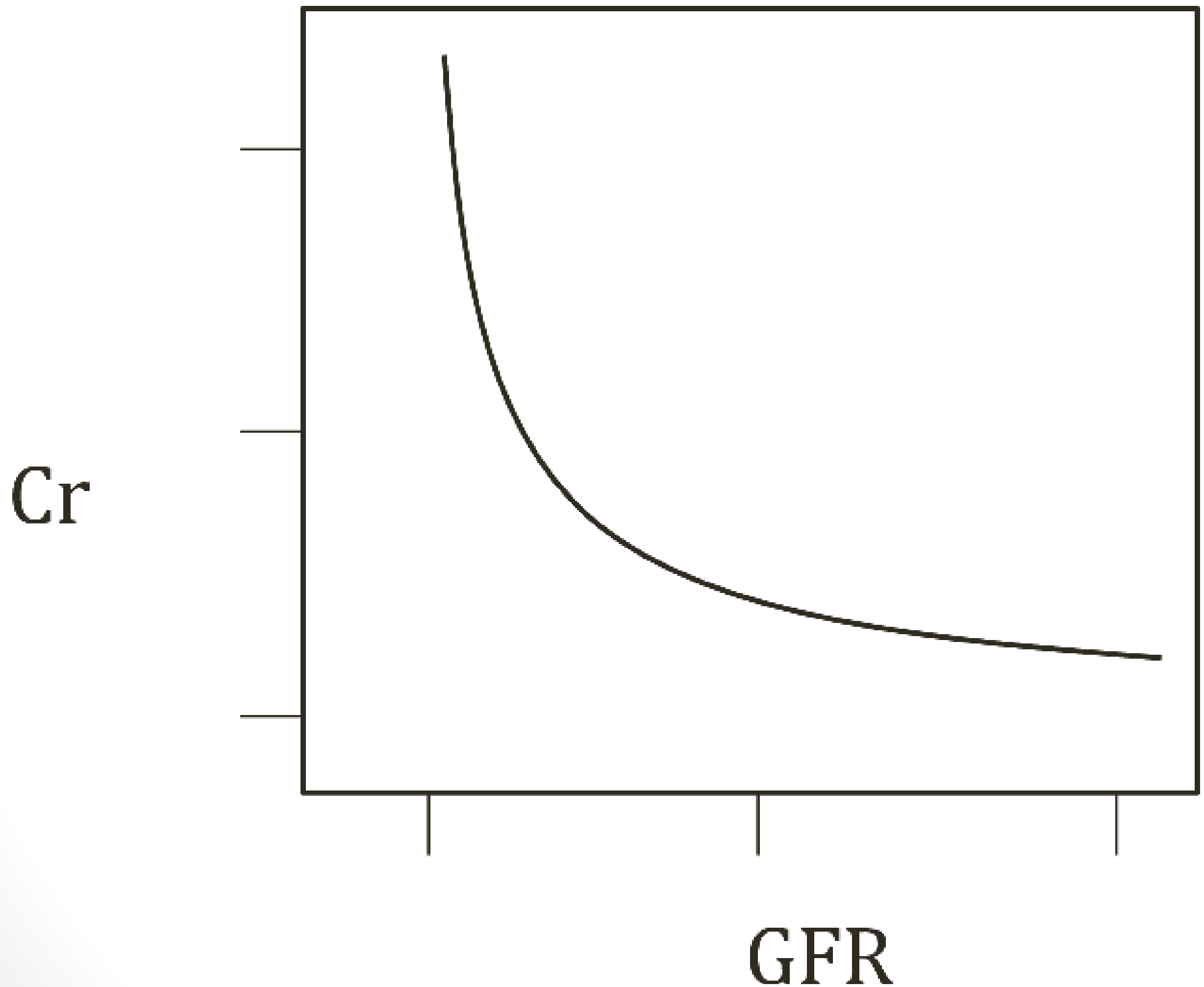
$$C_{Cr} = \frac{\overbrace{U_{Cr} * V}^{\substack{\text{Amount of Cr out in urine} \\ \text{Equal to amount produced}}}}{P_{Cr}} = GFR$$

Creatinine Clearance

$$C_{Cr} = \frac{\text{Constant}}{P_{Cr}} \approx \text{GFR}$$

Double [Cr] (1.0 to 2.0) → Half the GFR

Creatinine



Creatinine

- Worsening renal function = high blood Cr level
- Some sample values:
  - Normal kidney function → Cr = 0.8 mg/dl
  - Chronic kidney disease → Cr = 2.0 mg/dl
  - End stage renal disease (dialysis) → Cr = 4.0mg/dl

Creatinine

- **GFR declines with age**
  - Not always accompanied by rise in Cr
  - Use of formulas is key
  - Must adjust some medication dosages

Public Domain

<u>Cockcroft-Gault</u>

CrCl = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)

Forces that control GFR :

1. Hydrostatic pressure gradient across capillary wall

2.Osmotic pressure gradient across capillary wall

3.Permeability of the glomerukar capillaries

4.Effective filtration surface area.

Forces favoring filtration:

1.Hydrotatic pressure in glomerular capillary, = 50 mmHg

2.Osmotic pressure of protein in the filtrate = 0 mmHg

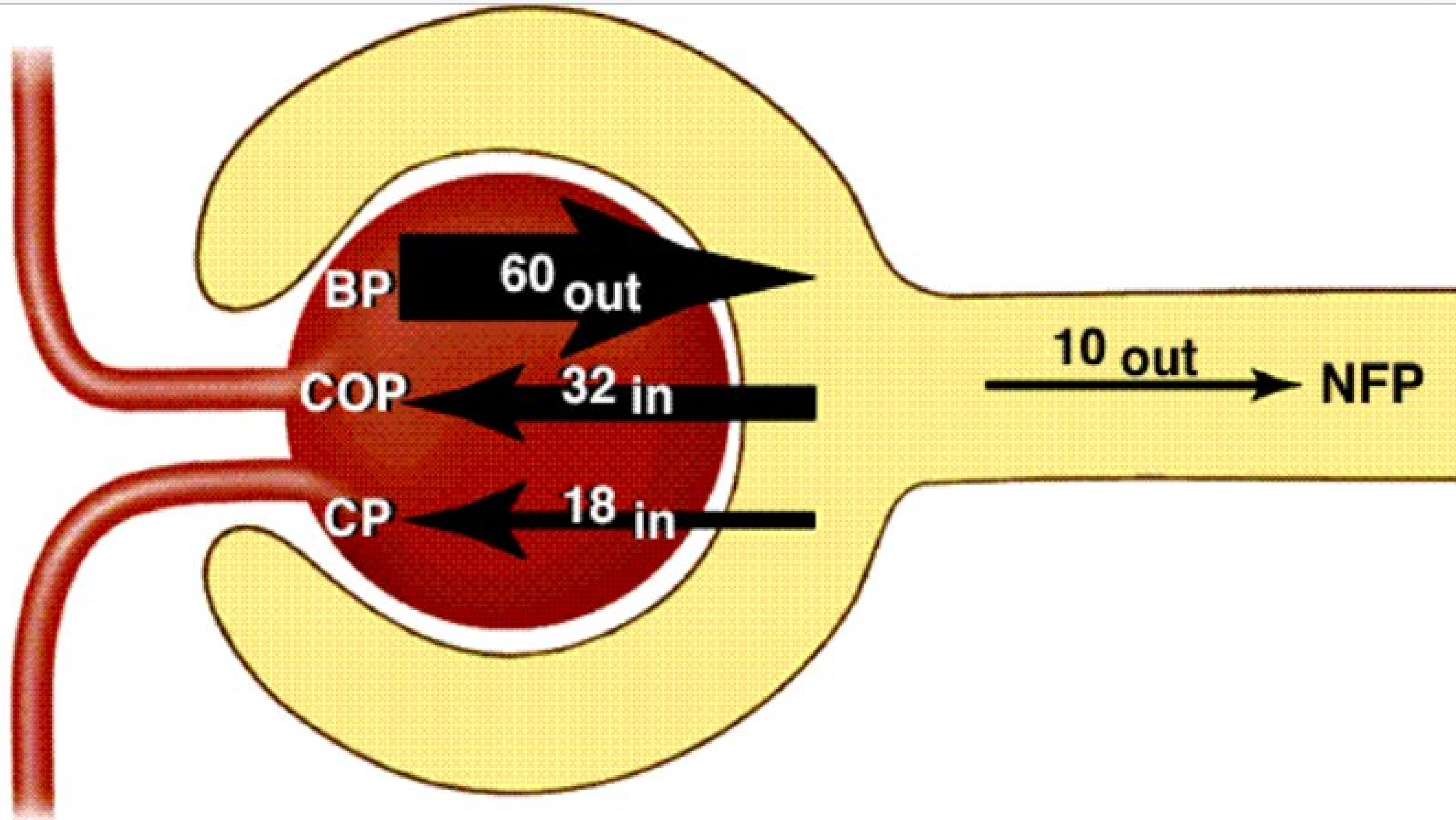
Forces opposing filtration

Hydrostatic pressure in Bowman's capsule = 18 mmHg

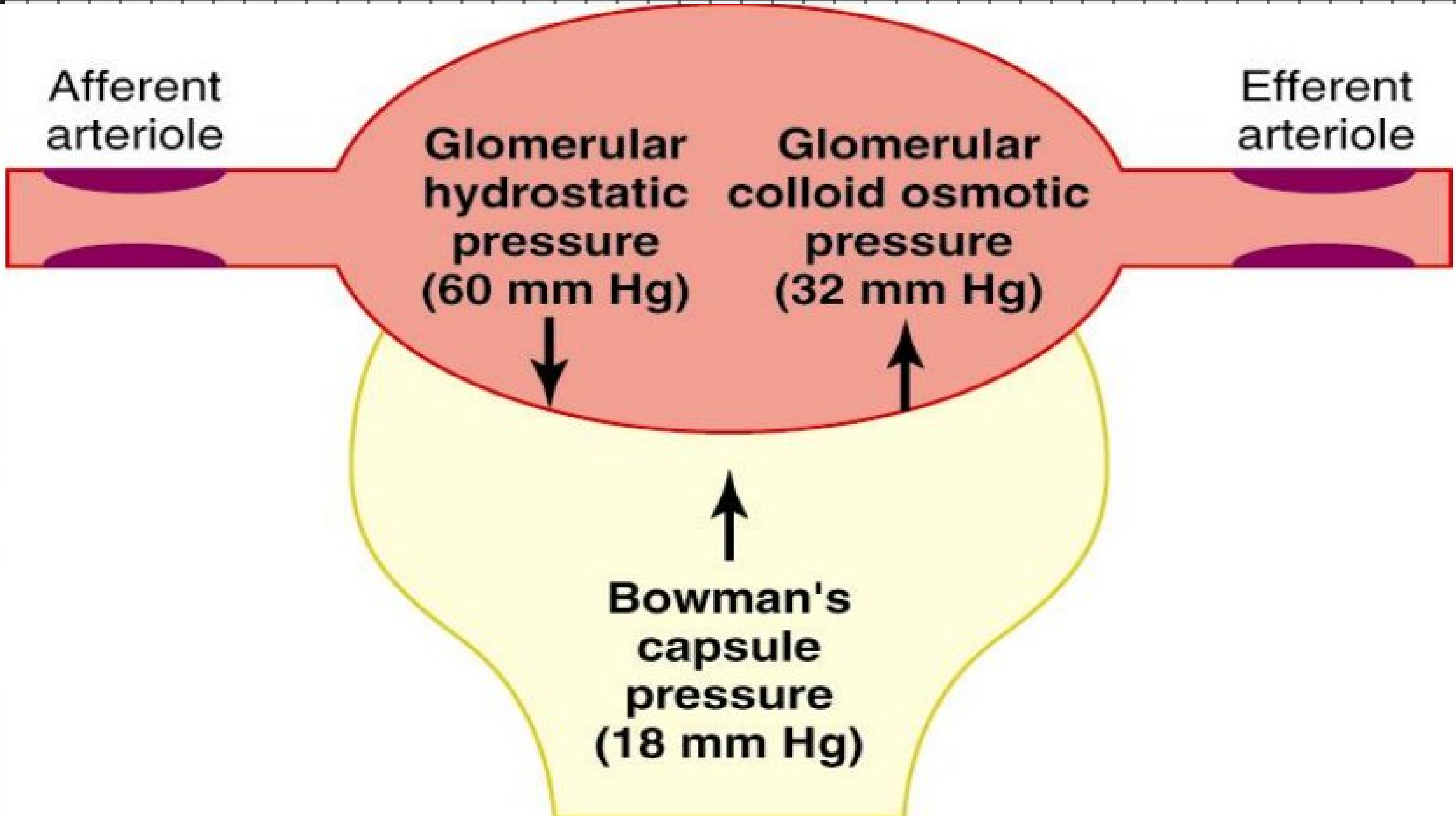
2. Osmotic pressure of plasma protein in glomerular capillary = 32 mmHg

The net filtering pressure = 60-50= 10 mmHg

Net filtration pressure = (P GC - P BS) - (GC - BS) (60- 18) – (32-0) +10 mm Hg



Capillary blood pressure (BP)	60 mmHg out
Colloid osmotic pressure (COP)	− 32 mmHg in
Capsular pressure (CP)	− 18 mmHg in
Net filtration pressure (NFP)	10 mmHg out



Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure − Bowman's capsule pressure − Glomerular oncotic pressure

GFR = 125 ml/min., 180 l/day

Glomerular capillary has higher filtration than other capillaries because of high P_G & large K_f

Filtration fraction= GFR/RBF

Net filtration pressure = $P_G - P_B - \pi_G + \pi_B$

=10 mmHg

GFR= Kf x $(P_G - P_B - \pi_G + \pi_B)$

$GFR = Kf \times (P_G - P_B - \pi_G + \pi_B)$

$125 = Kf \times (60-18-32+0)$

$Kf = 12.5 ml/min/mmHg$

Determination of GFR

GFR is determined by:

GFR= Kf x net filtration Pr.

Net filtration=Sum of hydrostatic pr. and colloid osmotic pr. across GBM .

$(P_G - P_B - \pi_G + \pi_B)$

Kf= surface area of Glomerular capillaries. (filtering and permeability).

Kf=12.5 ml/min/mm Hg

P_{G}= Hydrostatic pressure inside the glomerular capillaries which promotes filtration.

P_{B}= the hydrostatic pressure in Bowman's capsule outside the capillaries, which opposes filtration.

π_{G} = colloid osmotic pressure of the glomerular capillary plasma proteins , which opposes filtration.

π_{B} = the colloid osmotic pressure of the proteins in Bowman's capsule , which promotes filtration.

FILTRATION FRACTION

The Kf cannot be measured directly.

Estimated experimentally by:

K_f = GFR/net filtration pressure =12.5 ml/min/ mmHg

Pathophysiology: decreased number of functional glomerular capillary (surface area) or increased wall thickness$\rightarrow \downarrow K_f \rightarrow \downarrow$GFR

Like: HTN, DM, renal disease.

FACTORS AFFECTING GLOMERULAR FILTRATION RATE

1. Filtration coefficient (Kf).
2. Hydrostatic pressure in Bowman's space fluid (PBS)
3. Glomerular capillary hydrostatic pressure (PGC).
4. Glomerular capillary oncotic pressure (πGC).
5. Sympathetic stimulation
6. State of glomerular membrane

A patient is found to have elevated angiotensin II concentration. What effect would this have on glomerular hydrostatic Pressure?

Increased. What is the mechanism

Efferent arteriolar constriction .

A patient is placed on NSAID for OA, what effect would this have on glomerular hydrostatic pressure?

Decreased. What is the mechanism?

Inhibition of PG which normally keeps the afferent arteriole open

A patient with DM is found to have a BP of 145/95. He is started on ACE-I . What effect would this have on Glomerular hydrostatic pressure?

Decreased what is the mechanism ?

Inhibition of angiotensin II which mediate tonic control of the efferent arteriole .

Concerning the measurement of renal plasma flow (RPF) and GFR, which of the following are true?

A.Inulin concentration in the proximal tubule'slumen increases progressively as water is reabsorbed in the segment of the nephron

B.PAH(para-amino hippuric acid) is a good marker of renal plasma flow because it is freely filtered and is rapidly secreted by the proximal tubule, as a result very little PAH reach the renal vein

C.Inulin is a good GFR marker because it is freely filtered in the glomeruli and is not reabsorbed or secreted by the renal tubules.

D.A and C are correct

E.All are correct

1.Filtration coefficient (Kf)

Increased Kf raises GFR & Decreased Kf reduces GFR. Kf = permeability X filtration area (glomerular capillary membrane)   Hypoxia and presence of toxic agents and increase in colloidal osmotic pressure of bowmen's space increase Kf by increasing permeability   Sialoprotein have negative charge so anions have less permeability and size more than 8 nm will not filtered. Thickening of capillary membrane will decrease permeability