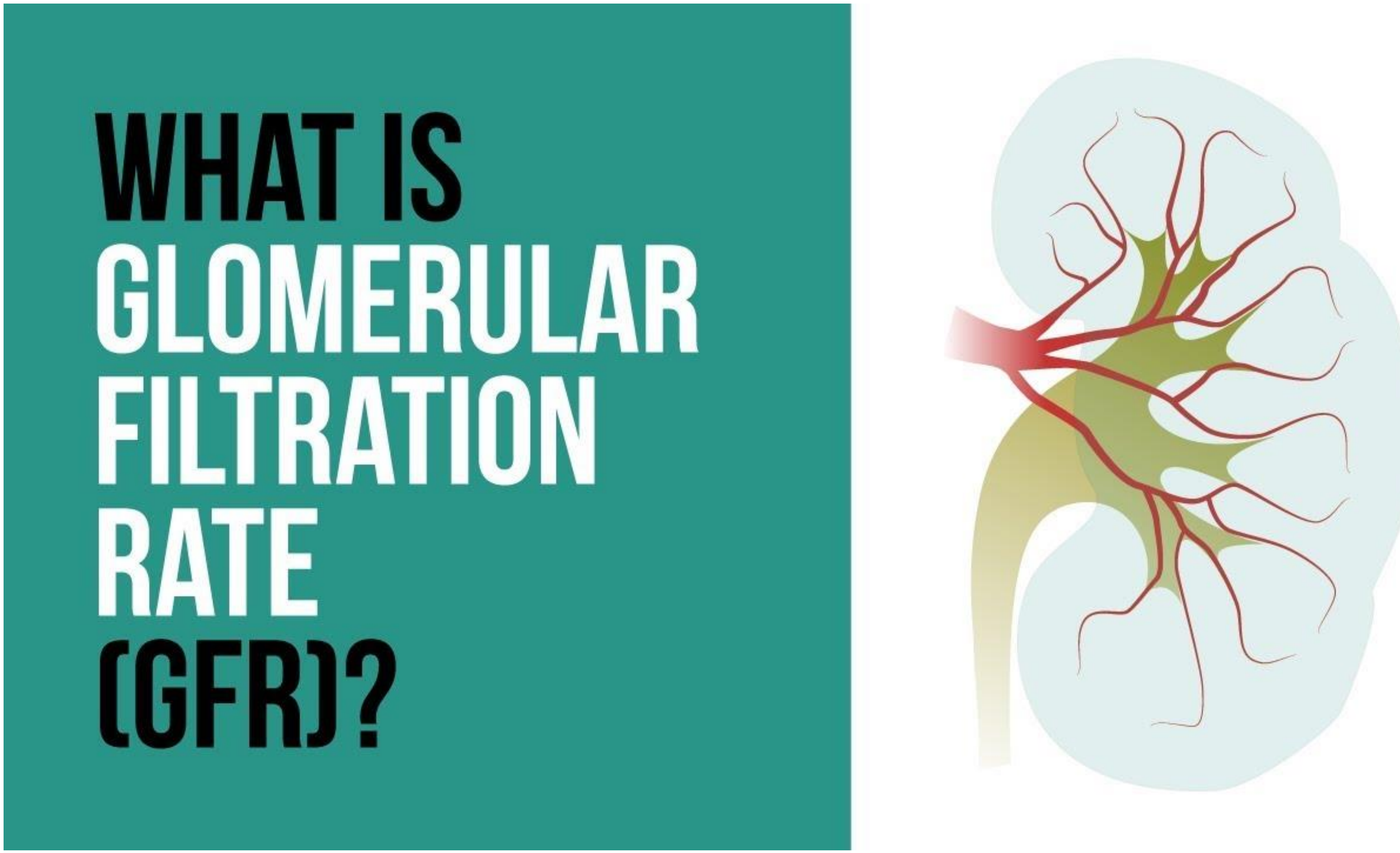
GFR lecture for second year students by Dr Riffat

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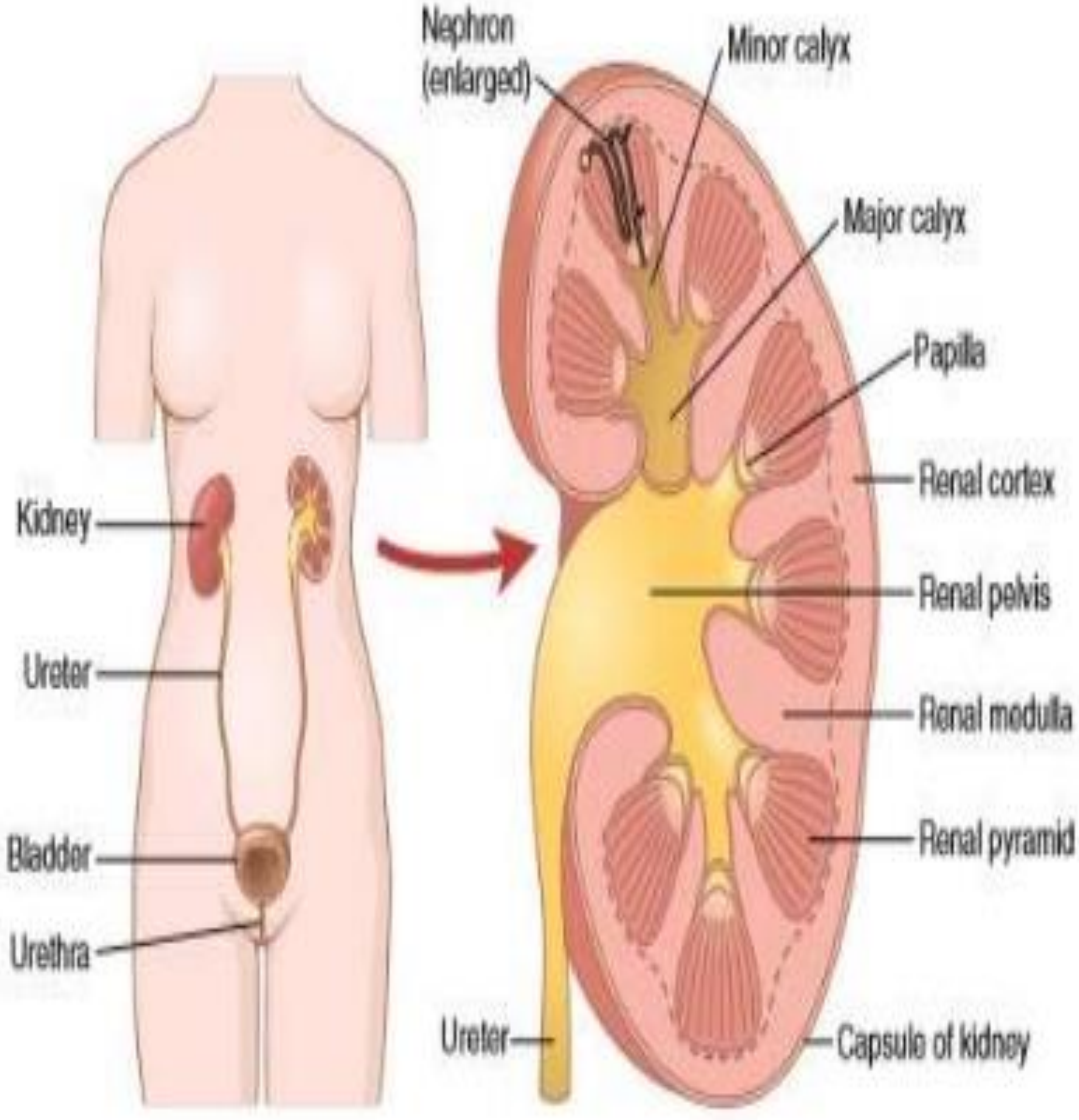
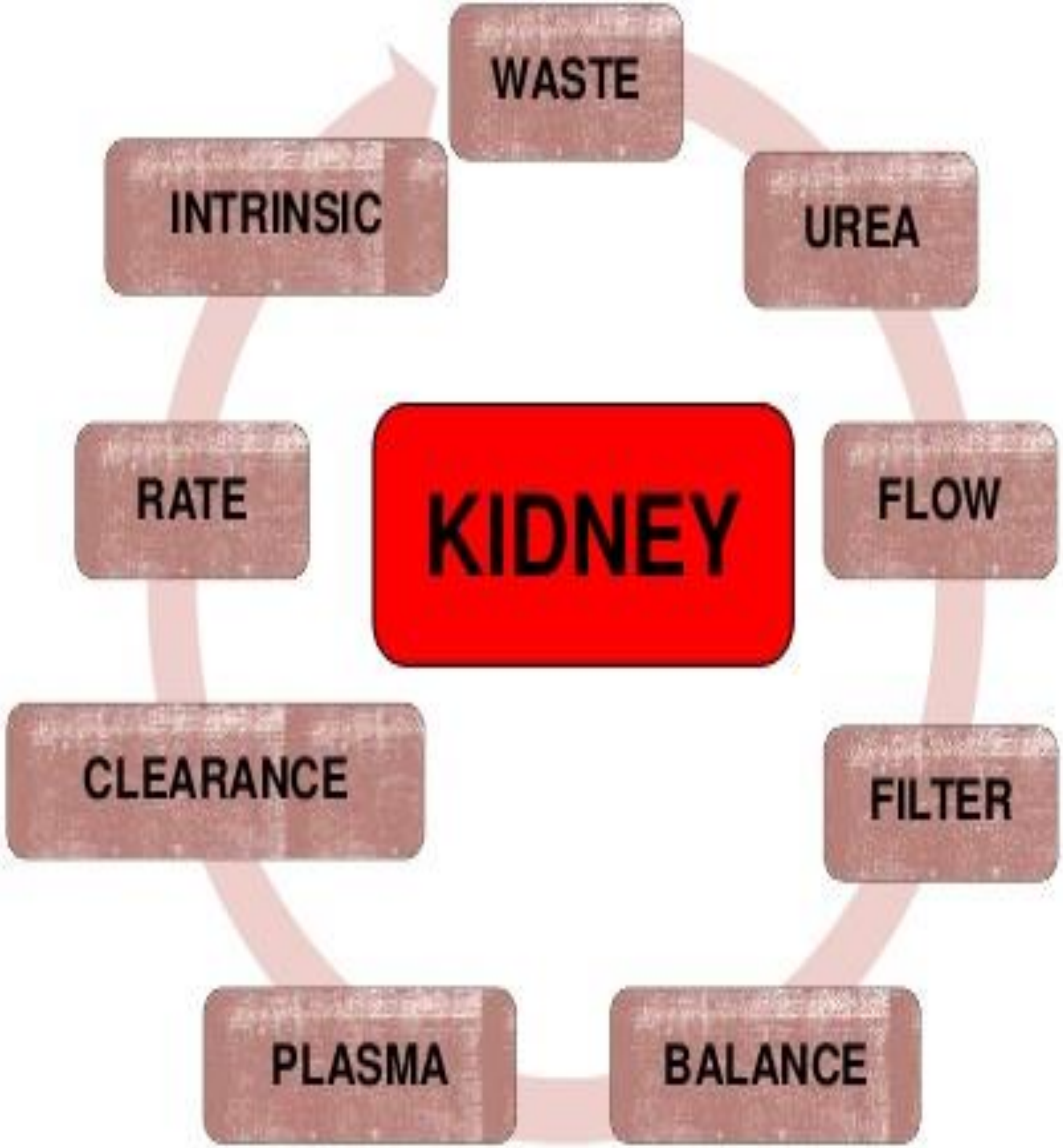


- A retroperitoneal organ
- T11-L3
- Normal size: 11-15cm in adults.
- Right kidney usually shorter than the left (upper limit of variation in length between right & left 1.5 cm)


WASTE
UREA
FLOW
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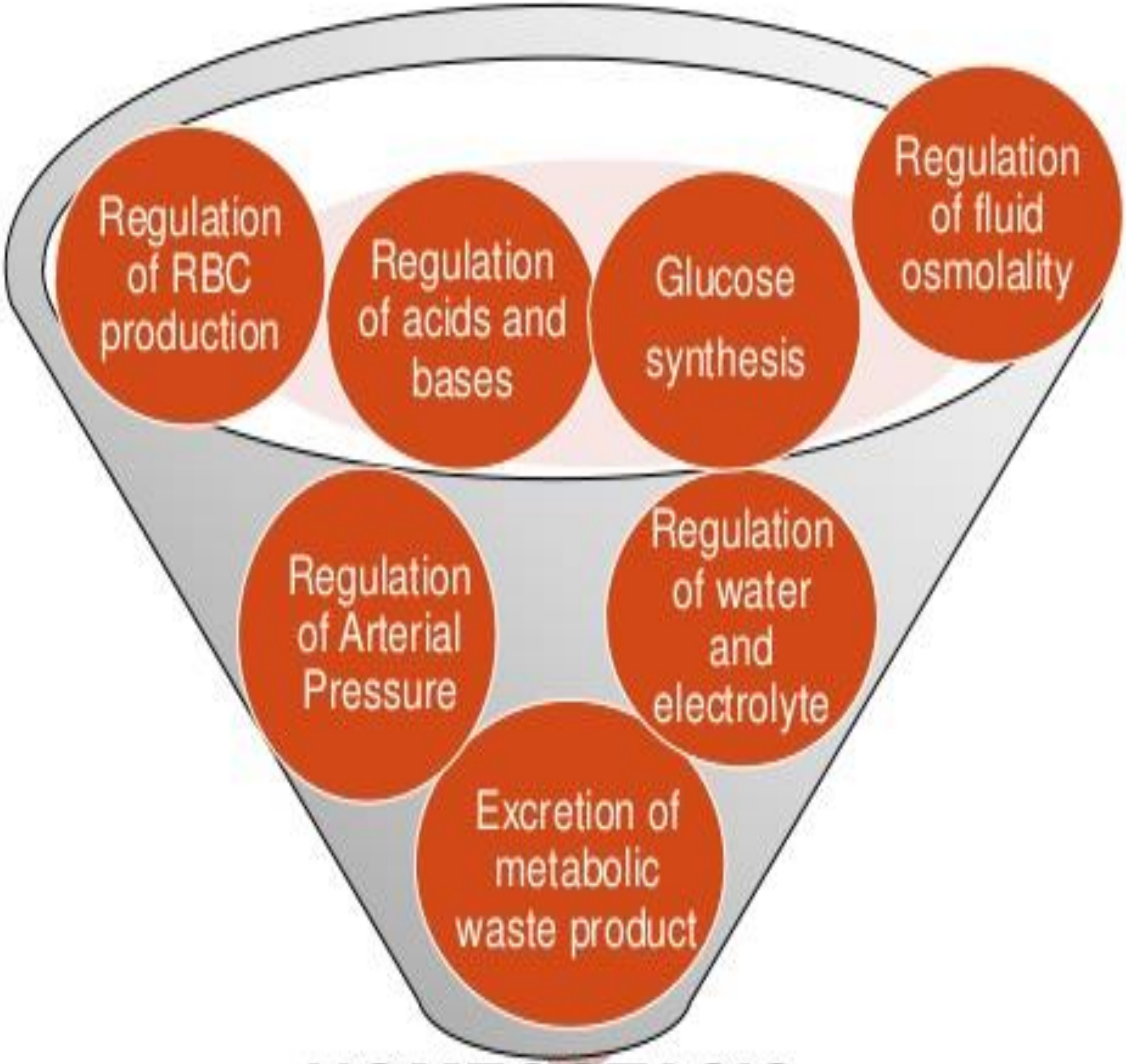
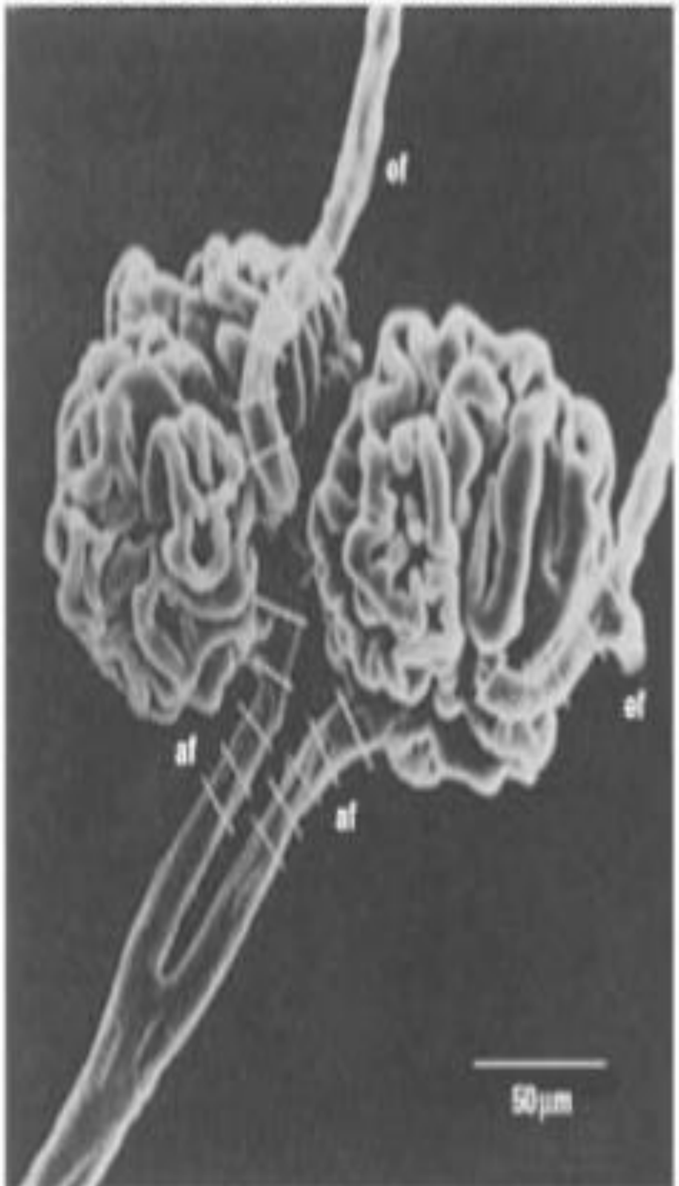
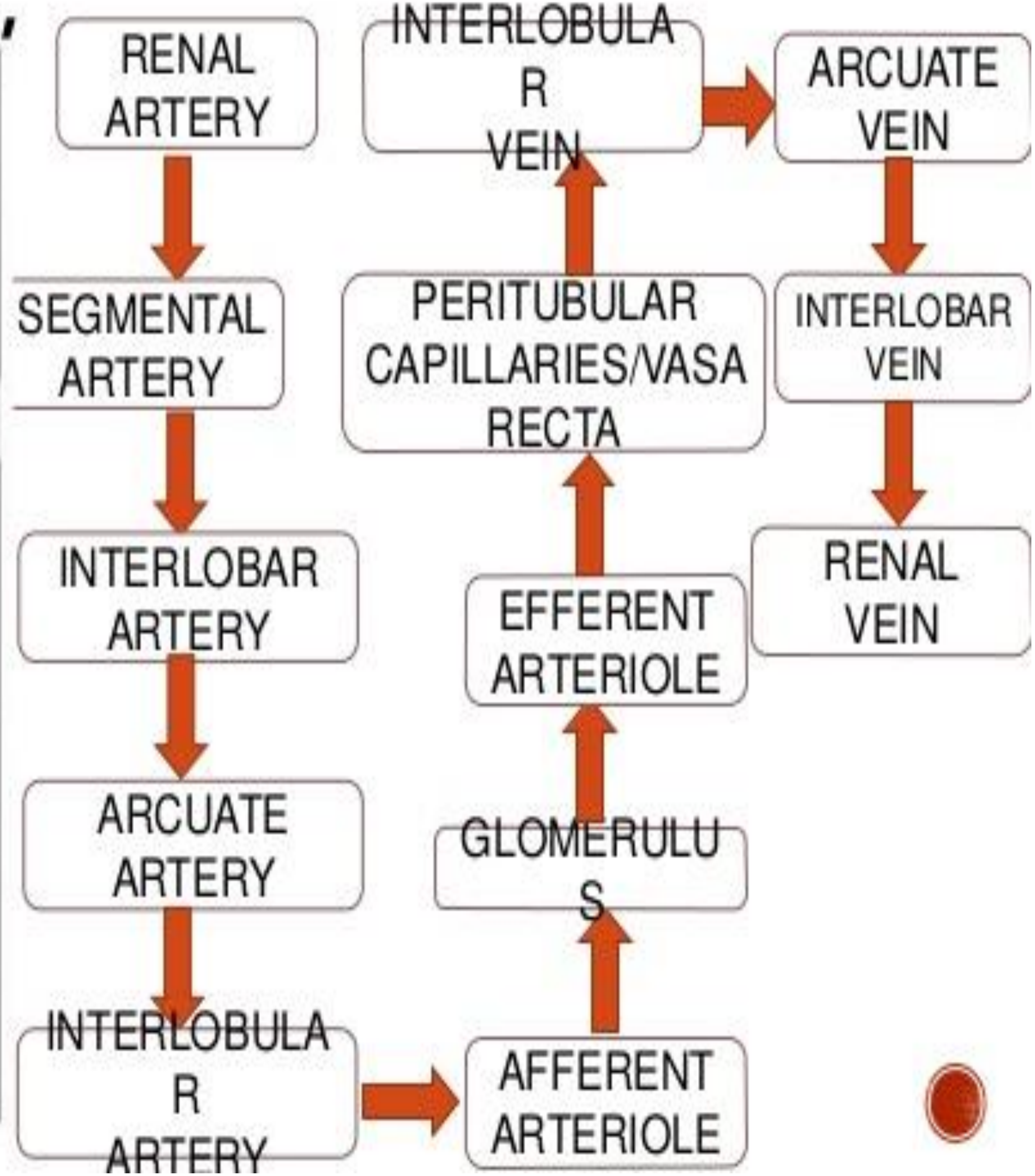
BALANCE
PLASMA
CLEARANCE
RATE
INTRINSIC
KIDNEY



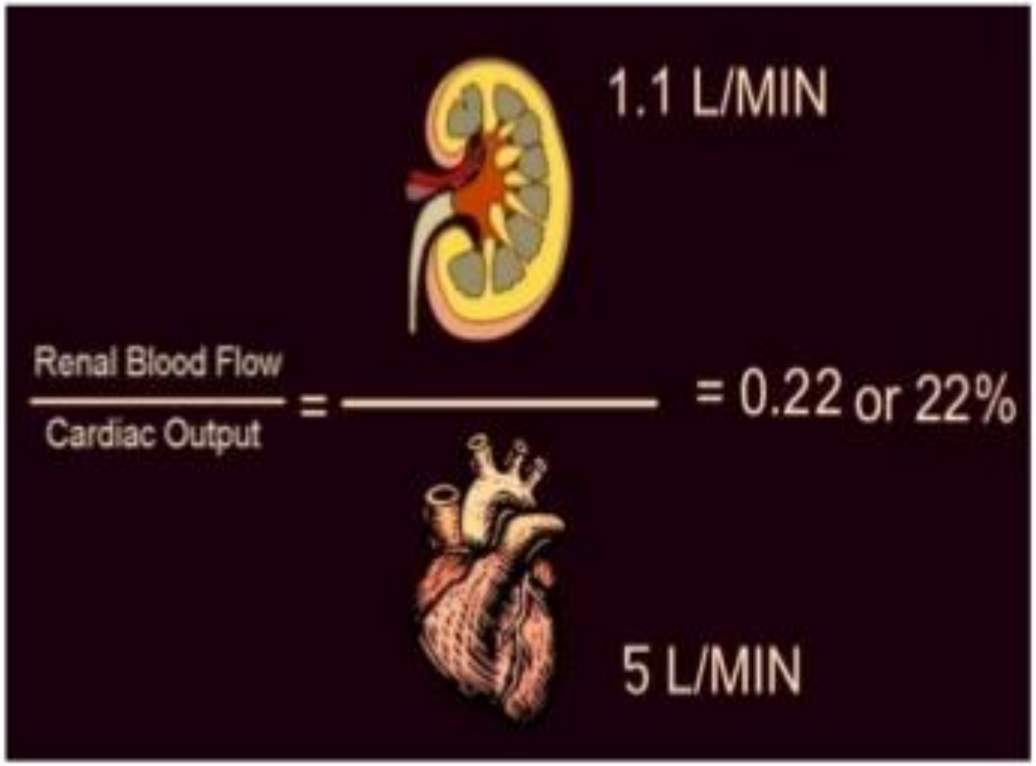
HOMEOSTASIS

Renal blood supply





Magnitude of Renal Blood Flow



- There is a large renal blood flow (RBF) at rest, equivalent to 1/5 of CO (1 L/min) to an organ that weighs 0.4% of body weight.
- Per unit mass, RBF at rest is higher than that to heart muscle or brain.
- The purpose of this additional flow is to supply enough plasma for the high rates of glomerular filtration that are necessary for precise regulation of body fluid volumes and solute concentrations.

- GFR is the volume of fluid filtered from ALL THE NEPHRONS OF BOTH KIDNEYS,the filtration is from the glomerular capillaries into the Bowman’s capsule IN ONE MINUTE
- it is cumulative performance of all functioning nephrons ….the most reliable marker of functioning renal mass ▪GFR influenced by age, sex
- ▪GFR also varies by a number of other variables ▪time of day, protein intake, pregnancy, extracellular fluid status, blood pressure extremes, use of anti-hypertensives

Why Are Large Amounts of Solutes Filtered and Then Reabsorbed by the Kidneys?

Advantages of a high GFR :

- **Rapid removal of waste products** from the body that depend primarily on glomerular filtration for their excretion.

- **Filtration of body fluids by the kidney many times each day**. Because the entire plasma volume is only about **3 liters**, whereas the **GFR** is about **180 L/day**, the entire plasma can be filtered and processed about **60 times each day**. This high GFR allows the kidneys to precisely and rapidly control the volume and composition of the body fluids.

Importance of GFR Autoregulation in Preventing Extreme Changes in Renal Excretion

- Normally, GFR is about 180 L/day and tubular reabsorption is 178.5 L/day, leaving 1.5 L/day of fluid to be excreted in the urine.
- In the absence of autoregulation, a relatively small increase in blood pressure (from 100 to 125 mm Hg) would cause a similar 25 per cent increase in GFR (from about 180 to 225 L/day).
- If tubular reabsorption remained constant at 178.5 L/ day, this would increase the urine flow to 46.5 L/day (the difference between GFR and tubular reabsorption)— a total increase in urine of more than 30-fold.
- Because the total plasma volume is only about 3 liters, such a change would quickly deplete the blood volume.
- It happens by a mechanism called **Glomerulotubular Balance** (The Ability of the Tubules to Increase Reabsorption Rate in Response to Increased Tubular Load)

GLOMURULARFILTRATION RATE

- **DEFINITION:**

  The fluid that filters through the glomerulus into bowman`s capsule is called "glomerular filtration".
- **NORMAL VALUE:**

  125ml/min

Table 24. Normal GFR in Children and Young Adults

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m^2)
1 week (males and females)	40.6 ±14.8
2–8 weeks (males and females)	65.8 ±24.8
>8 weeks (males and females)	95.7 ±21.7
2–12 years (males and females)	133.0 ±27.0
13–21 years (males)	140.0 ±30.0
13–21 years (females)	126.0 ±22.0

Renal Blood Flow and O_2 Consumption

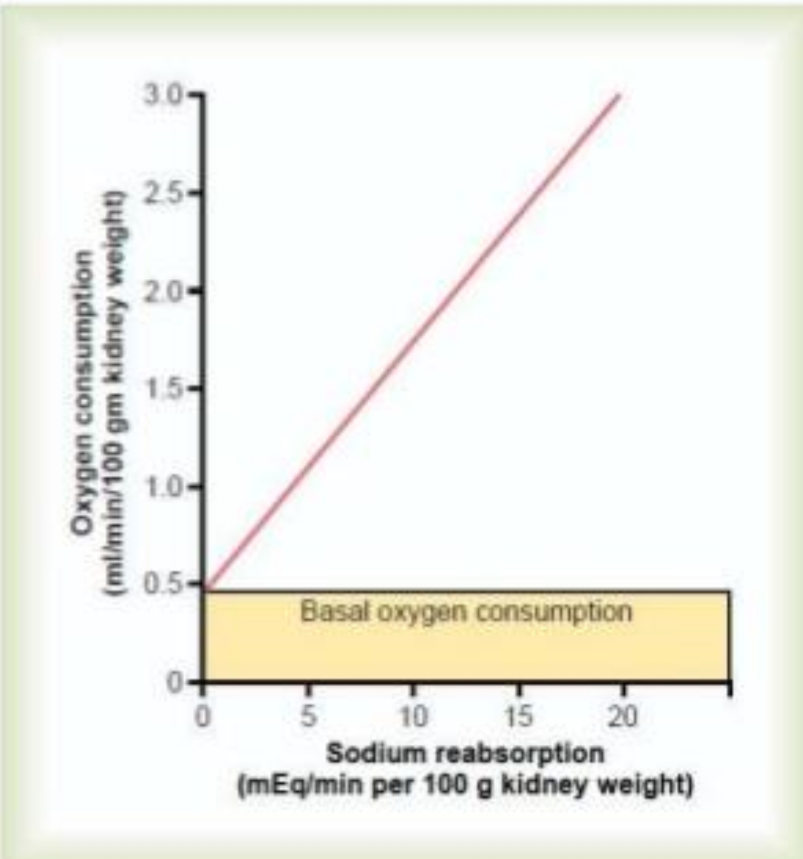


Fig.: Relationship between O_2 consumption and Na reabsorption in dog kidneys.

- On a per gram weight basis, the kidneys normally consume O_2 at twice the rate of the brain but have almost 7 times the blood flow of the brain.
- A large fraction of the O_2 consumed by the kidneys is related to the high rate of active Na reabsorption by the renal tubules. If RBF and GFR are reduced and less Na is filtered, less Na is reabsorbed and less O_2 is consumed.
- If glomerular filtration completely ceases, renal Na reabsorption also ceases, and O_2 consumption decreases to about ¼th normal. This residual O_2 consumption

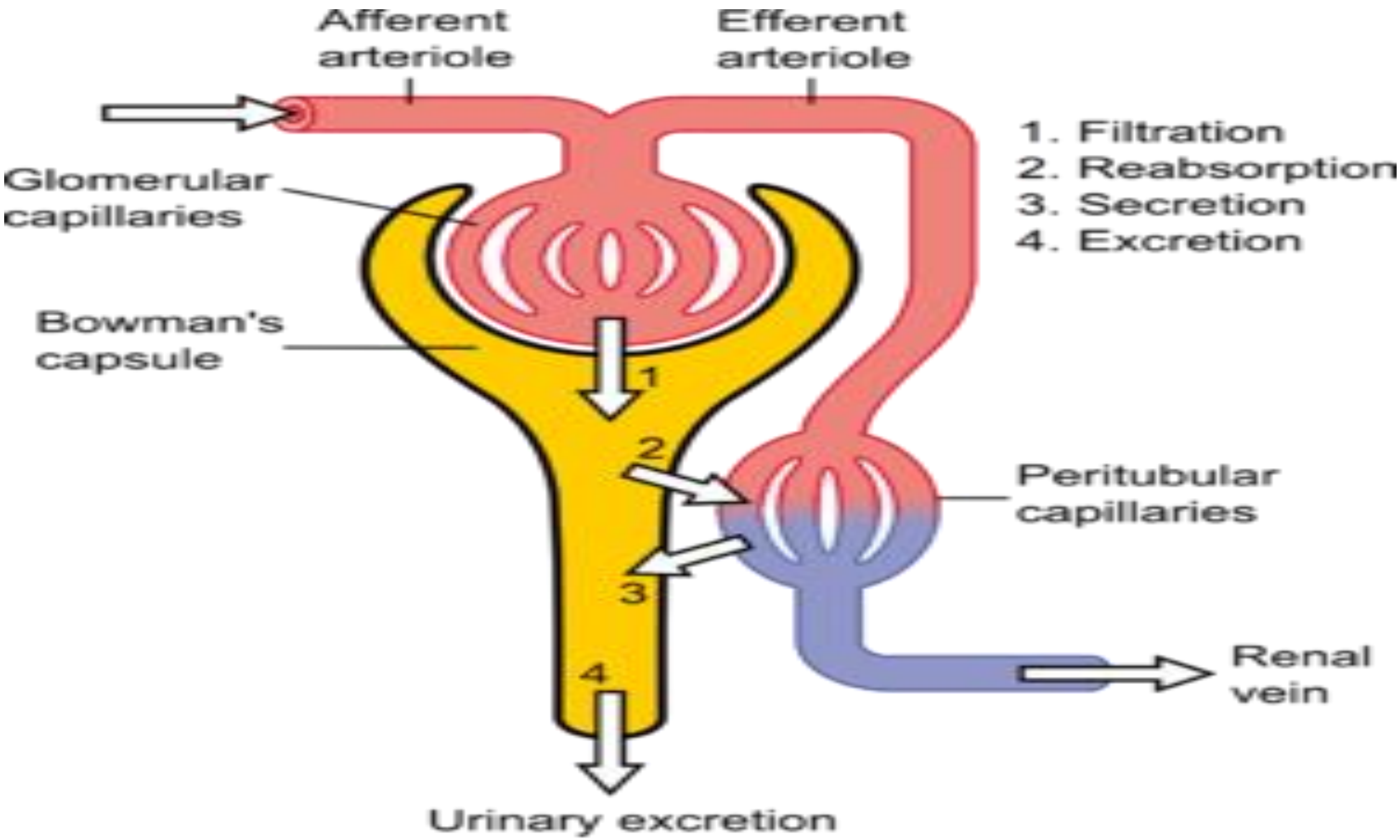
DETERMINANTS OF RENAL BLOOD FLOW

- Renal blood flow is determined by the pressure gradient across the renal vasculature (the difference between renal artery and renal vein hydrostatic pressures), divided by the total renal vascular resistance:

$$\frac{(\text{Renal artery pressure} - \text{Renal vein pressure})}{\text{Total renal vascular resistance}}$$

Approximate Pressures and Vascular Resistances in the Circulation of a Normal Kidney

Vessel	Pressure in Vessel (mm Hg) Beginning	End	Per Cent of Total Renal Vascular Resistance
Renal artery	100	100	~0
Interlobar, arcuate, and interlobular arteries	~100	85	~16
Afferent arteriole	85	60	~26
Glomerular capillaries	60	59	~1
Efferent arteriole	59	18	~43
Peritubular capillaries	18	8	~10
Interlobar, interlobular, and arcuate veins	8	4	~4
Renal vein	4	~4	~0



Excretion = Filtration – Reabsorption + Secretion

Composition of the Glomerular Filtrate

- The glomerular filtrate is essentially protein-free and devoid of cellular elements, including red blood cells.
- The concentrations of other constituents of the glomerular filtrate, including most salts and organic molecules, are similar to the concentrations in the plasma.
- Exceptions to this generalization include a few low-molecular-weight substances, such as calcium and fatty acids, that are not freely filtered because they are partially bound to the plasma proteins. Almost one half of the plasma calcium and most of the plasma fatty acids are bound to proteins, and these bound portions are not filtered through the glomerular capillaries.

GFR Is About 20 Per Cent of the Renal Plasma Flow

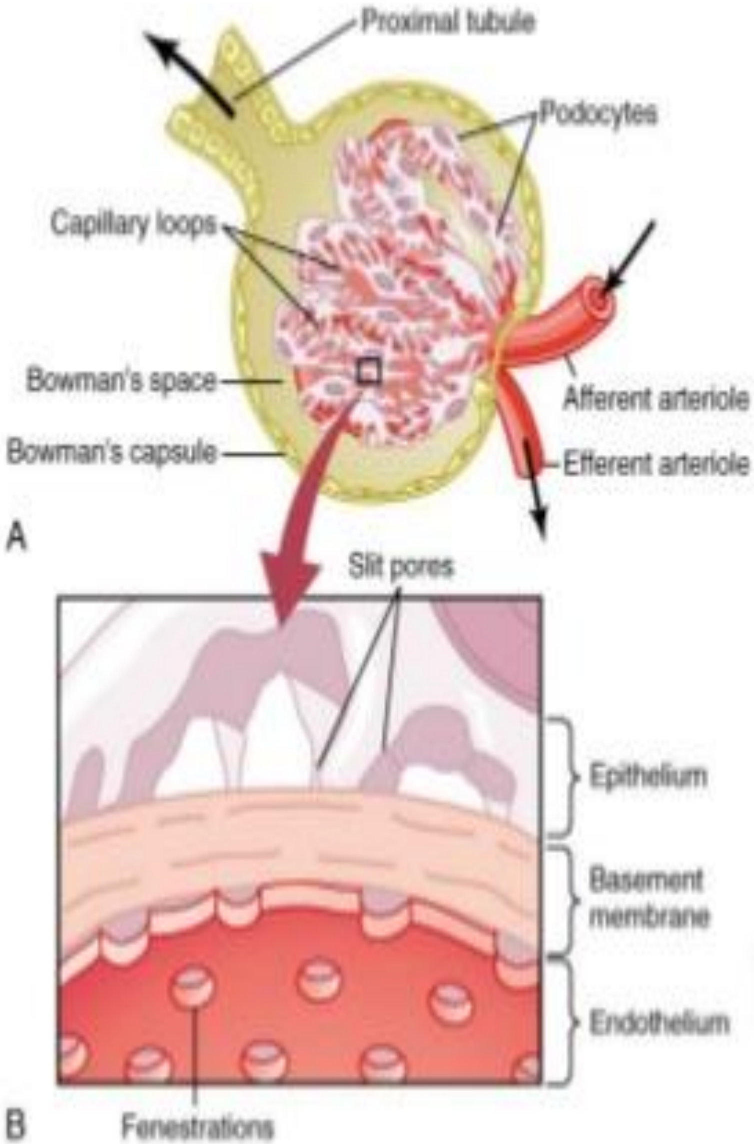
- The fraction of the renal plasma flow that is filtered (the filtration fraction) averages about 0.2; this means that about 20 per cent of the plasma flowing through the kidney is filtered through the glomerular capillaries.
- The **filtration fraction** is calculated as follows:

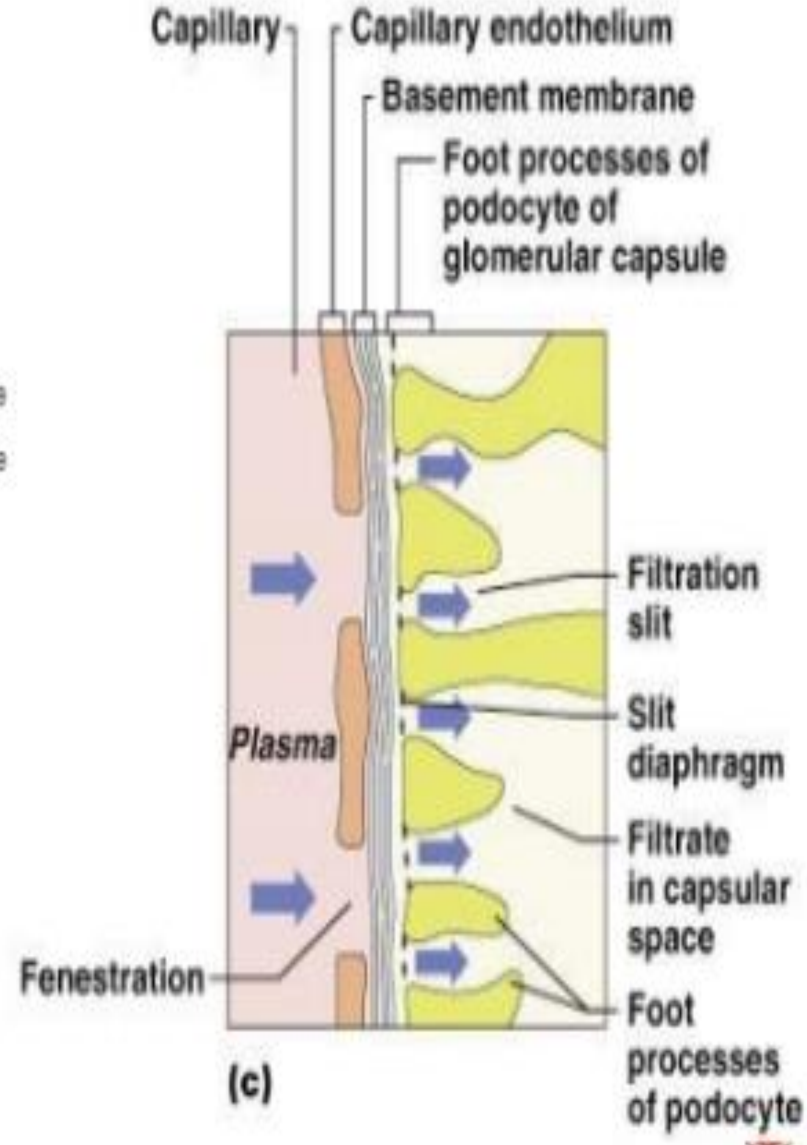
  Filtration fraction = GFR/Renal plasma flow

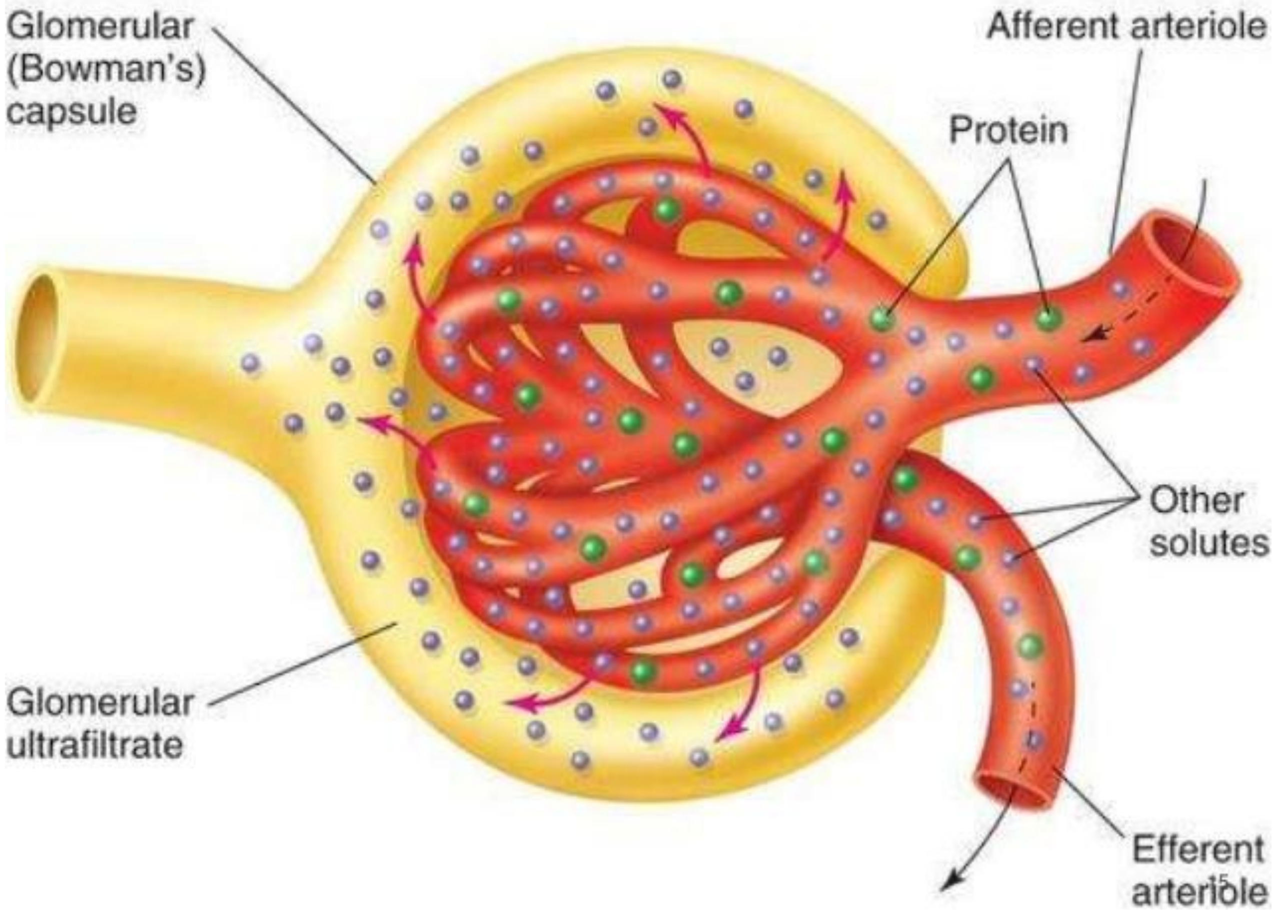
GLOMERULAR FILTRAION

- **MEMBRANES THROUGH WHICH FILTRATION TAKES PLACE:**
- ***T***he endothelial layer of the capillary→(fenestrae).
- ***B***asement membrane(it self is a meshwork)
- ***L***ayer of the epithelial cells →bowman`s capsule.

GLOMERULAR FILTRATION BARRIER






Glomerular (Bowman's) capsule
Afferent arteriole
Protein
Other solutes
Glomerular ultrafiltrate
Efferent arteriole

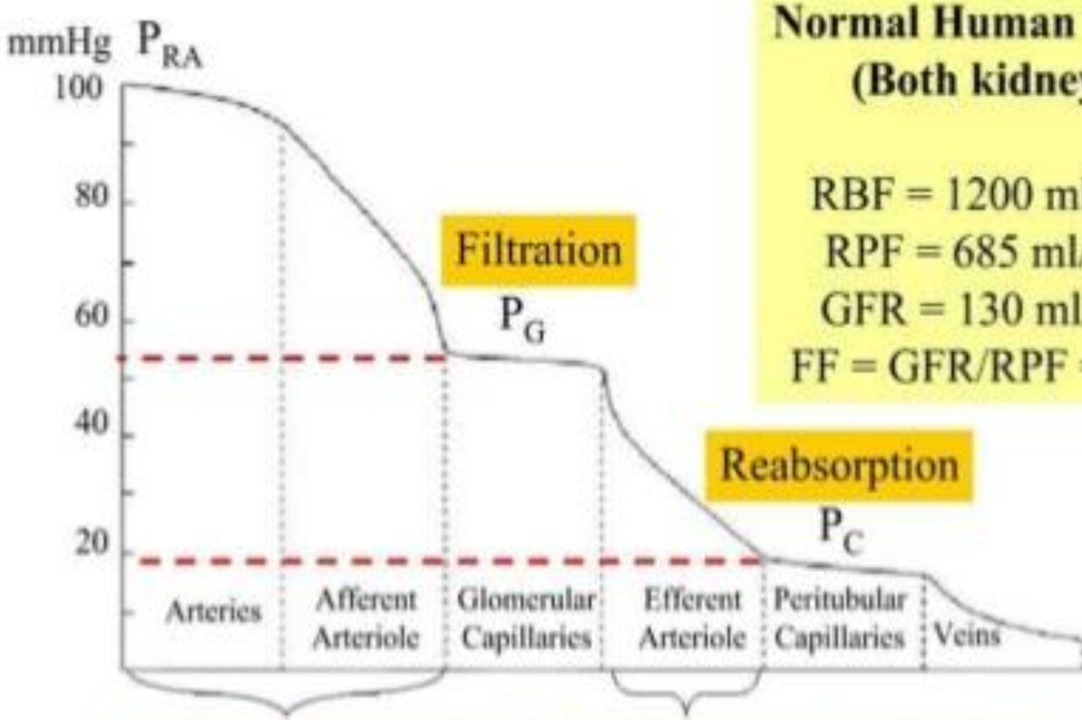
FILTERABILITY OF SOLUTES IS INVERSELY RELATED TO THEIR SIZE.

Filterability of Substances by Glomerular Capillaries Based on Molecular Weight

Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

A filterability of 1.0 means that the substance is filtered as freely as water; a filterability of 0.75 means that the substance is filtered only 75 per cent as rapidly as water.

Representative hydrostatic pressure profile along nephrovascular unit



Normal Human Values (Both kidneys)

RBF = 1200 ml/min
RPF = 685 ml/min
GFR = 130 ml/min
FF = GFR/RPF = 0.19

$R_A = P_{RA} - P_G / RBF$

$R_A = (100 - 54)/1200$

$R_E = P_G - P_C / RBF - GFR$

$R_E = (54 - 18)/(1200 - 130)$

R_A = Afferent arteriolar resistance

R_E = Efferent arteriolar resistance

P_{RA} = Renal arterial pressure

P_G = Glomerular pressure

P_C = Peritubular capillary pressure

RBF = Renal blood flow

RPF = Renal plasma flow

FF = Filtration fraction

GFR CALCULATIONS

- **GFR CALCULATION:**

GFR= NET FILTRATION PRESSURE . Kf

→***G***FR = 10 mmHg . 12.5 ml/min/mmHg

→***G***FR = 125ml/min.

IMPORTANT VALUES

- **FILTRATION COEFFICIENT (Kf):**

  *T*he glomerular filtration rate in both kidneys per milli-meter of mercury of filtration pressure.

- **NORMAL VALUE:**

  →12.5 ml/min/mmHg.

FILTRATION FRICTION RATE

- **FILTRATION FRICTION RATE:** ***A***mount of fluid that filter through the bowman`s capsule membrane per mint.
- **NORMAL VALUE:** 125ml/min
- **CALCULATON:**

F.F = GFR/R.P.F(renal plasma flow)

→**F**.F = 125ml/min/600ml/min

→**F**.F = 0.2 , 20%

IMPORTANT VALUES

- **FILTRATION COEFFICIENT (Kf):**

  The glomerular filtration rate in both kidneys per milli-meter of mercury of filtration pressure.

- **NORMAL VALUE:**

  →12.5 ml/min/mmHg.

REGULATION OF GFR

- **ONCOTIC PRESSURE:**

  The forces of proteins molecules to attract water molecules because ,

- ***T***he proteins have charges
- ***A***cts as a polar substance
- ***L****i*ke albumin

There are two oncotic pressures one in glomerulus and one in bowman`s capsule

- Oncotic pressure is represented by I<(PIE)
- Eg. I< Gc – I< BC

REGULATION OF GFR

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  The forces of proteins molecules to attract water molecules because ,

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There are two oncotic pressures one in glomerulus and one in bowman`s capsule

- Oncotic pressure is represented by I<(PIE)
- Eg. I< Gc – I< BC

REGULATION OF GFR

- **1.PLASMA ONCOTIC PRESSURE/ GLOMERULAR ONCOTIC PRESSURE/ I<(pie)Gc:**

- **F**orce which keeps water in glomerulus

- **R**everse force/pressure of filtration.

- **NORMAL VALUE:** 28 mmHg.

GREGULATION OF GFR

- **ONCOTIC PRESSURE IN BOWMANS CAPSULE/ I< Bc:**

- **N**o proteins in bowman`s capsule
- **B**ut very low amount of amino acids.
- **I**n healthy person no pressure is present

- **NORMAL VALUE:** = 0(zero)

REGULATION OF GFR

- **HYDROSTATIC PRESSURE:** **P**ressure of fluid exerted on the wall of vessels/capillaries.
- **W**e have two hydrostatic pressures one bowman`s capsule and one glomeruluar.
- **H**ydrostatic pressure is represented by = “P”
- Eg PBc - PGc

REGULATION OF GFR

- **HYDROSTATIC PRESSURE IN THE BOWMAN`S SPACE / PBc:**

- **F**luid pressure which oppose the filtration.
- **I**ts about 10mmHg

Determinants of the GFR

The GFR is determined by :-

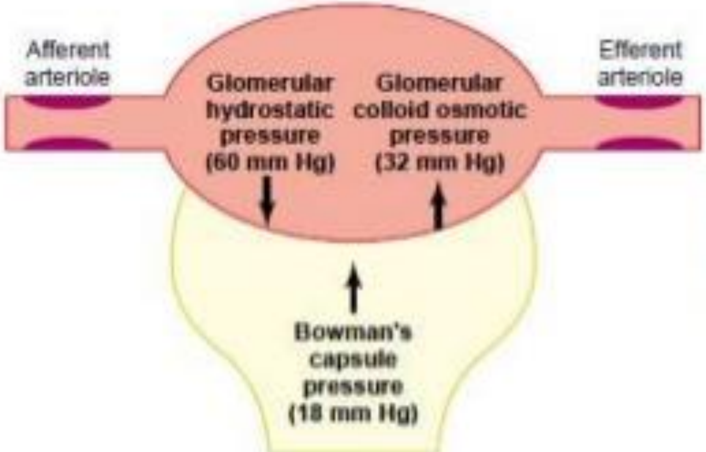
(1) The sum of the hydrostatic and colloid osmotic forces across the glomerular membrane, which gives the ***net filtration pressure***, *and*

(2) The **glomerular capillary filtration coefficient, K_f**.

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

$$GFR = K_f \times \text{Net filtration pressure}$$

DETERMINANTS OF THE GFR *CONTD' …*



Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) – Bowman's capsule pressure (18 mm Hg) – Glomerular oncotic pressure (32 mm Hg)

- **Forces Favoring Filtration (mm Hg)**
  Glomerular hydrostatic pressure = 60 mm Hg
  Bowman's capsule colloid osmotic pressure = 0 mm Hg
- **Forces Opposing Filtration (mm Hg)**
  Bowman's capsule hydrostatic pressure = 18 mm Hg
  Glomerular capillary colloid osmotic pressure = 32 mm Hg
- **Net filtration pressure** = 60 – 18 – 32 = +10 mm Hg

(1) Increased Glomerular Capillary Filtration Coefficient Increases GFR

- The K_f is a measure of the product of the hydraulic conductivity and surface area of the glomerular capillaries.

- Some diseases, however, lower K_f by reducing the number of functional glomerular capillaries (thereby reducing the surface area for filtration) or by increasing the thickness of the glomerular capillary membrane and reducing its hydraulic conductivity. For example, **chronic, uncontrolled hypertension** and **diabetes mellitus** gradually reduce K_f by increasing the thickness of the glomerular capillary basement membrane and, eventually, by damaging the capillaries so severely that there is loss of capillary function.

(2) Increased Bowman's Capsule Hydrostatic Pressure Decreases GFR

- In certain pathological states associated with **obstruction of the urinary tract**, Bowman's capsule pressure can increase markedly, causing serious reduction of GFR. For example, **precipitation of calcium or of uric acid** may lead to **"stones"** that lodge in the urinary tract, often in the ureter, thereby obstructing outflow of the urinary tract and raising Bowman's capsule pressure. This reduces GFR and eventually can damage or even destroy the kidney unless the obstruction is relieved.

The Ability of a Solute to Penetrate the Glomerular Membrane Depends on:

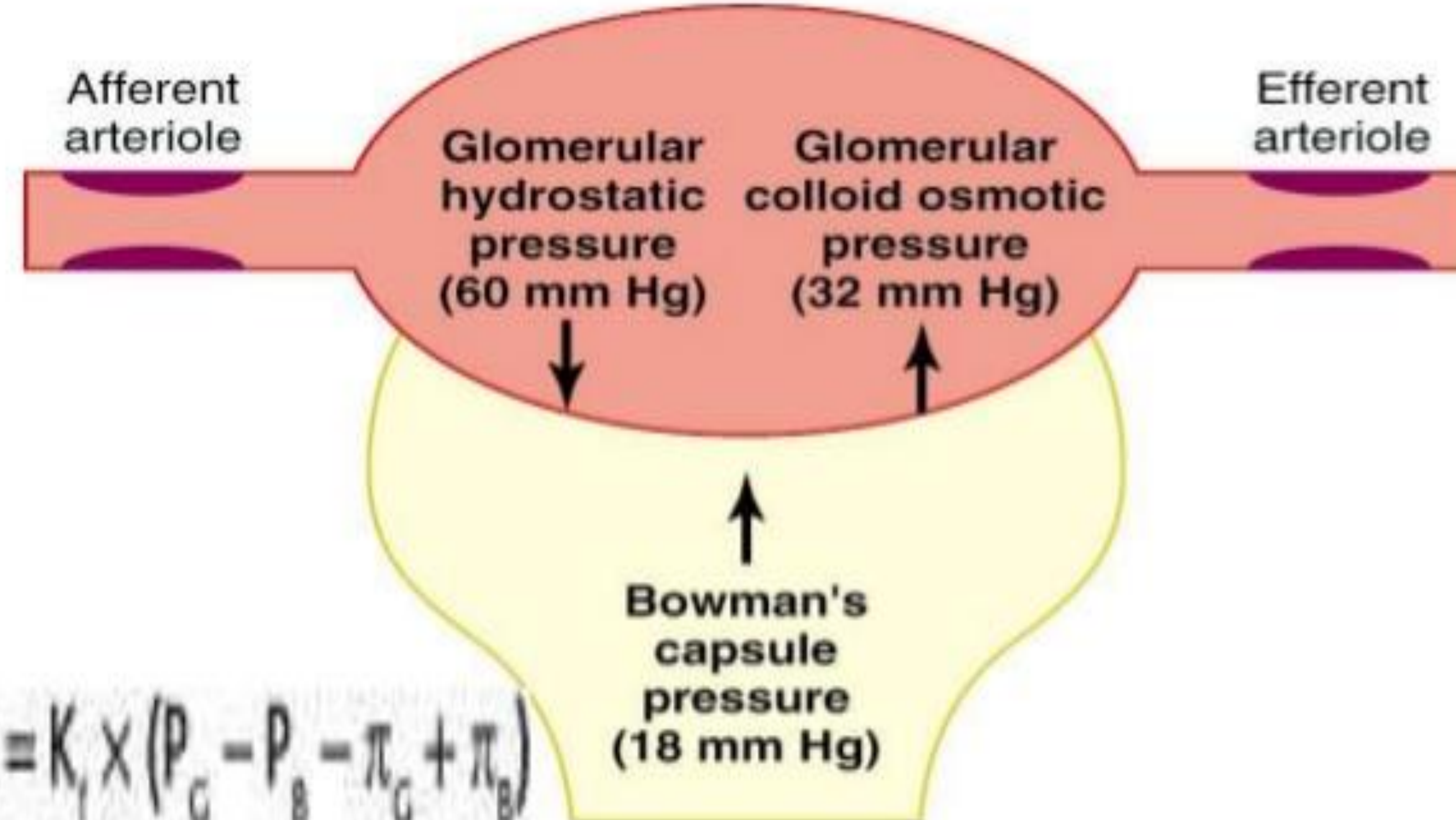
- **Molecular size** (small molecules > filterability)
- **Ionic charge** (cations > filterability)

GFR DETERMINANTS

Balance of hydrostatic and colloid osmotic forces acting across the capillary membrane

Capillary filtration coefficient (K_f), the product of the permeability and filtering surface area of the capillaries)

$GFR = K_f$ x Net Filtration Pressure



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

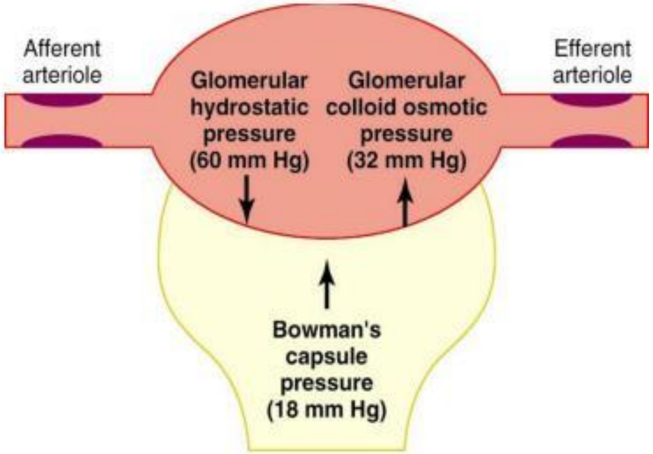
Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) − Bowman's capsule pressure (18 mm Hg) − Glomerular oncotic pressure (32 mm Hg)

Determinants of Glomerular Filtration Rate

Figure 26-12; Guyton and Hall

GFR = Kf x Net Filt. Press

- Kf is intrinsic permeability and surface area available of glomerulus-not really controllable, but number one reason why GFR changes
- NFP is the sum of the hydrostatic and colloid osmotic forces
- Note: Π_B is so low, can be considered zero
- Π_{GC} does change through glomerulus, but not big determinant



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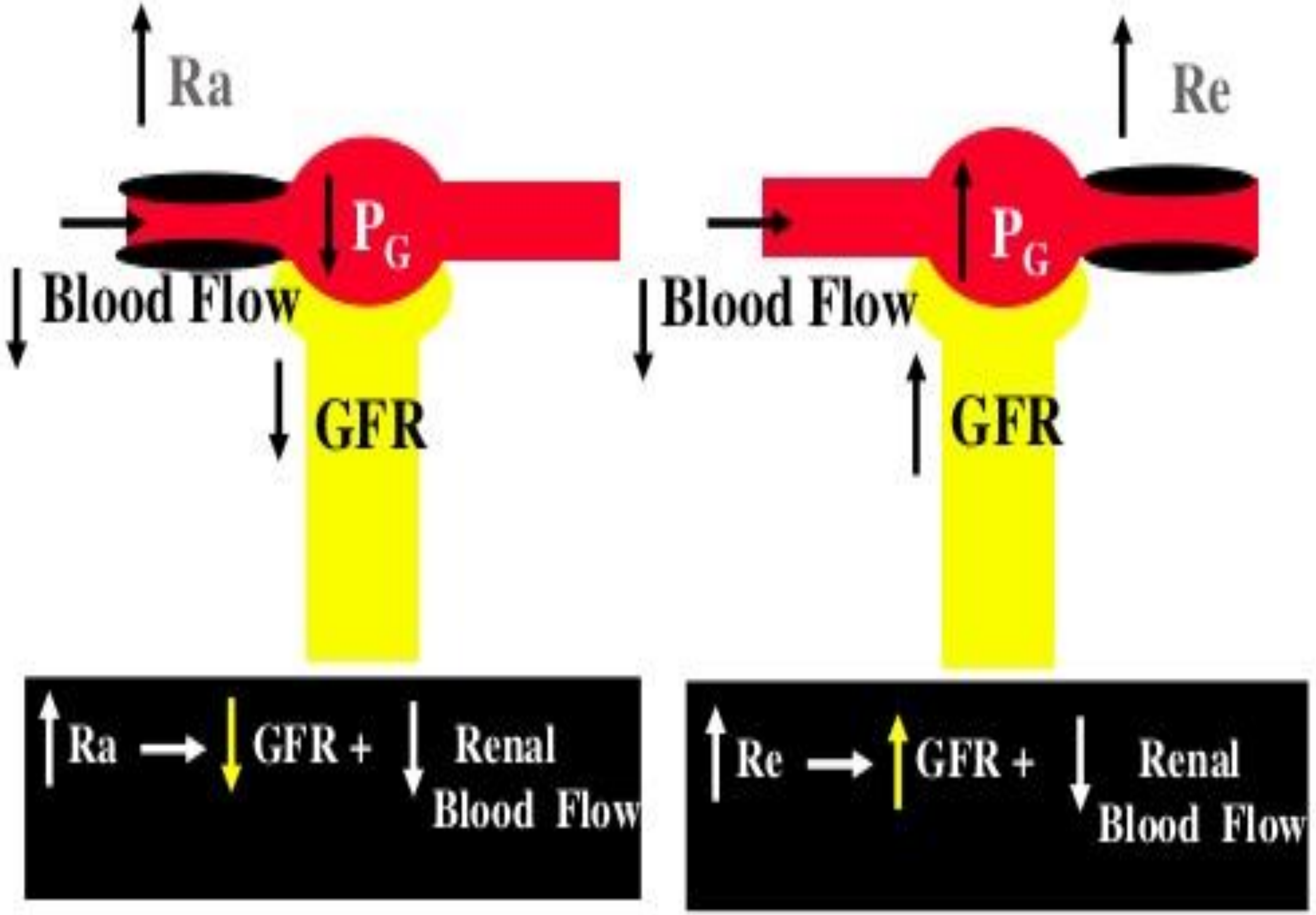
GLOMERULAR HYDROSTATIC PRESSURE (P_G)

- the determinant of GFR most subject to physiological control

- Factors that influence P_G
  - arterial pressure (effect is buffered by autoregulation)
  - afferent arteriolar resistance
  - efferent arteriolar resistance

Effect of Afferent and Efferent Arteriolar Constriction on Glomerular Pressure

$$Q = \frac{\Delta P}{R}$$



Summary of determinants of GFR

$\uparrow K_f \longrightarrow \uparrow$ GFR

$\uparrow P_B \longrightarrow \downarrow$ GFR

$\uparrow \Pi_G \longrightarrow \downarrow$ GFR

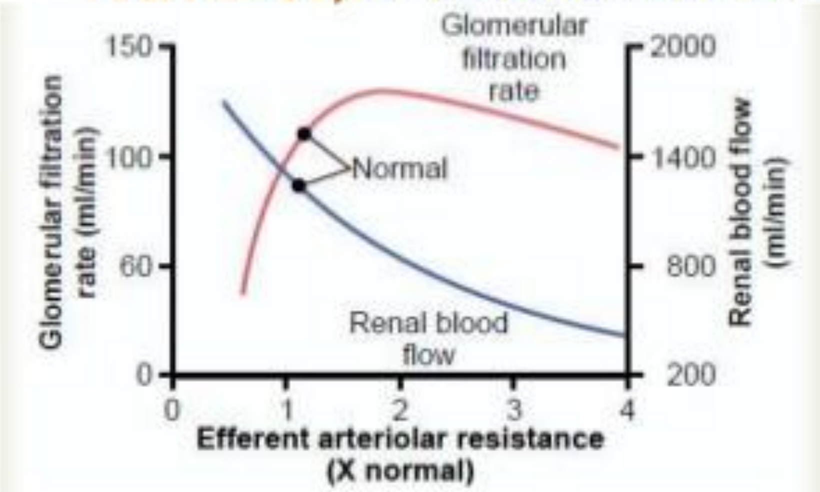
$\uparrow P_G \longrightarrow \uparrow$ GFR

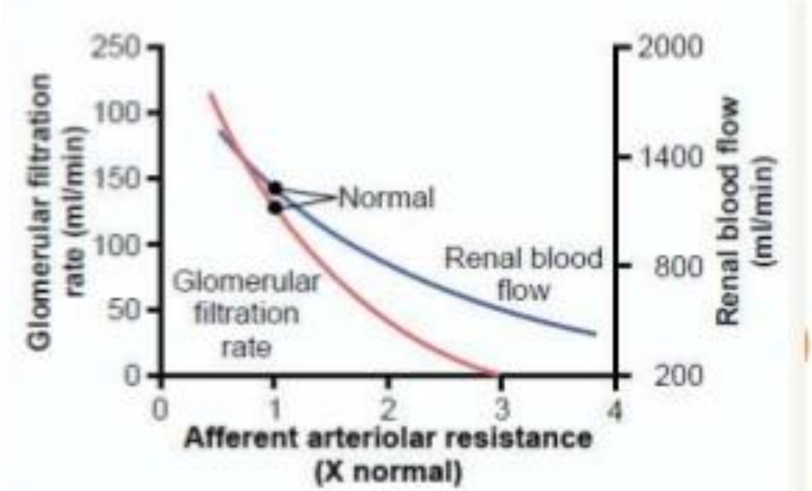
- $\uparrow R_A \longrightarrow \downarrow P_G \longrightarrow \downarrow$ GFR
- $\uparrow R_E \longrightarrow \uparrow P_G \longrightarrow \uparrow$ GFR

(as long as $\uparrow R_E$ < 3-4 x normal)

(4) Increased Glomerular Capillary Hydrostatic Pressure Increases GFR

- Glomerular hydrostatic pressure is determined by three variables, each of which is under physiologic control: (1) *arterial pressure, (2) afferent arteriolar resistance, and (3) efferent arteriolar resistance*.
- **Constriction of afferent arterioles reduces GFR**. However, the effect of efferent arteriolar constriction depends on the severity of the constriction; **modest efferent constriction raises GFR**, but **severe efferent constriction (more than a threefold increase in resistance) tends to reduce GFR**.





FACTORS THAT CAN DECREASE THE GLOMERULAR FILTRATION RATE (GFR)

Physical Determinants*	Physiologic/Pathophysiologic Causes
$\downarrow K_f \rightarrow \downarrow$ GFR	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow$ GFR	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow$ GFR	$\downarrow$ Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow$ GFR	
$\downarrow A_P \rightarrow \downarrow P_G$	$\downarrow$ Arterial pressure (has only small effect due to autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	$\downarrow$ Angiotensin II (drugs that block angiotensin II formation)
$\uparrow R_A \rightarrow \downarrow P_G$	$\uparrow$ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)

* Opposite changes in the determinants usually increase GFR.

K_f, glomerular filtration coefficient; P_B, Bowman's capsule hydrostatic pressure; π_G, glomerular capillary colloid osmotic pressure; P_G, glomerular capillary hydrostatic pressure; A_P, systemic arterial pressure; R_E, efferent arteriolar resistance; R_A, afferent arteriolar resistance.

Renal Hemodynamics

INTRINSIC

Control Mechanism:
Autoregulation
Tubuloglomerular Feedback

EXTRINSIC

Control Mechanism:
Sympathetic Nerves
Hormones
Composition of Blood

Sympathetic Nervous System Activation Decreases GFR

- Essentially all the blood vessels of the kidneys, including the afferent and the efferent arterioles, are richly innervated by sympathetic nerve fibers.
- Strong activation of the renal sympathetic nerves can constrict the renal arterioles and decrease renal blood flow and GFR.
- Moderate or mild sympathetic stimulation has little influence on renal blood flow and GFR.
- The renal sympathetic nerves seem to be most important in reducing GFR during severe, acute disturbances lasting for a few minutes to a few hours, such as those elicited by the defense reaction, brain ischemia, or severe hemorrhage. In the healthy resting person, sympathetic tone appears to have little influence on renal blood flow.

Importance of GFR Autoregulation in Preventing Extreme Changes in Renal Excretion

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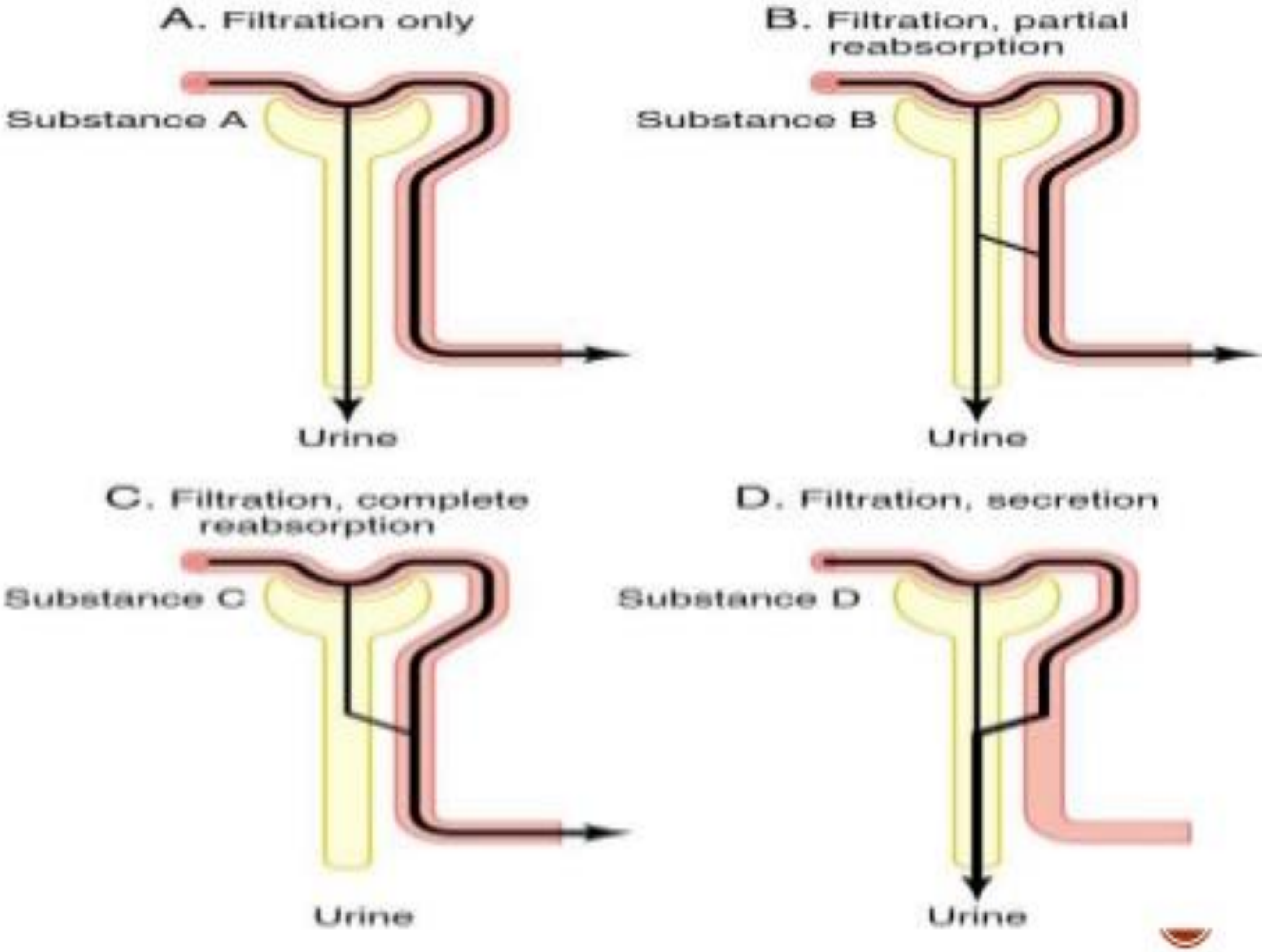
- Because the total plasma volume is only about 3 liters, such a change would quickly deplete the blood volume.
- It happens by a mechanism called **Glomerulotubular Balance** (The Ability of the Tubules to Increase Reabsorption Rate in Response to Increased Tubular Load)

• **Clearance** is a general concept that describes the rate at which substances are removed (cleared) from the plasma.



- GFR ▪GFR cannot be measured directly. ▪Most common method is based on the concept of clearance

Clearance Technique

Renal clearance of a substance is the volume of plasma <u>completely</u> cleared of a substance per min.

$$Cs \times Ps = Us \times V \qquad Cs = \frac{Us \times V}{Ps}$$

Where: **Cs** = clearance of substance S (mL/min)
Ps = plasma conc. of substance S (mg/mL)
Us = urine conc. of substance S (mg/mL)
V = urine flow rate (mL/min)

Use of clearance to measure GFR

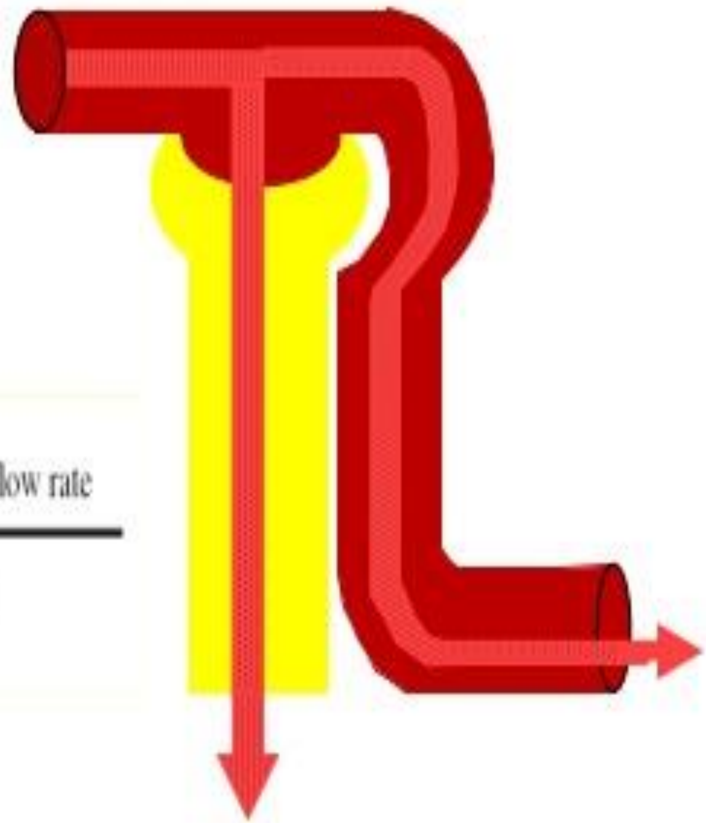
For a substance that is freely filtered, but not reabsorbed or secreted (inulin, ^{125}I-iothalamate, ~creatinine), **renal clearance is equal to GFR**

amount filtered = amount excreted

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

$$GFR = \frac{U_{in} \times V}{P_{in}}$$

$$GFR = \frac{[sub]_{urine} \times \text{urine flow rate}}{[sub]_{plasma}}$$



Calculation of GFR:

P_{inulin} = 1.0 mg / 100ml
U_{inulin} = 125 mg/100 ml
Urine flow rate = 1.0 ml/min

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

$$GFR = \frac{125 \times 1.0}{1.0} = 125 \text{ ml/min}$$