Urine Formation by the Kidneys: I. Glomerular Filtration, Renal Blood Flow and Their Control

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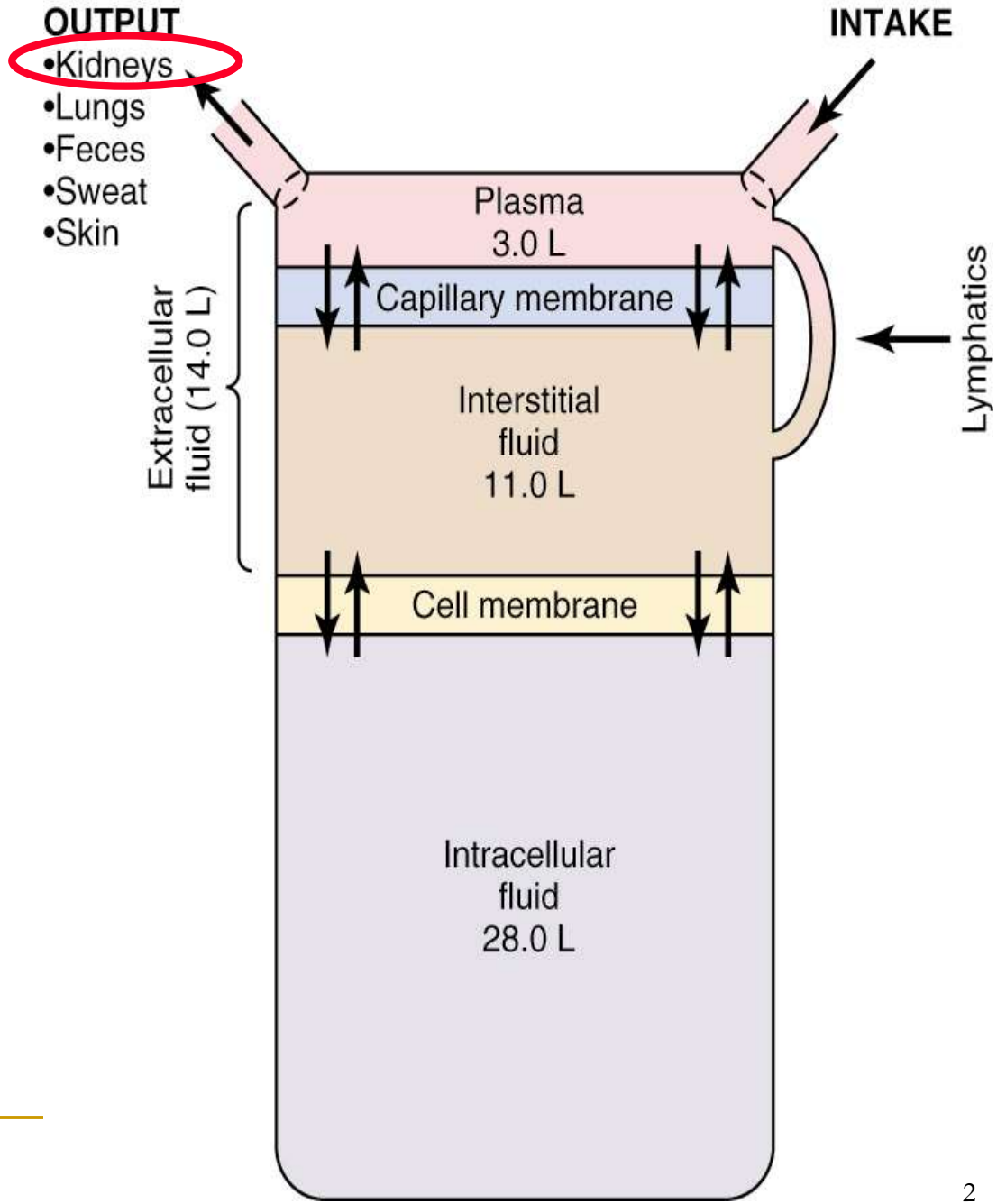
Body fluid regulation.



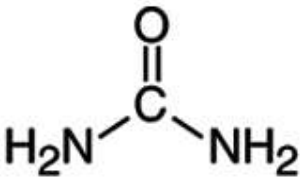
Renal System

Functions of kidney:

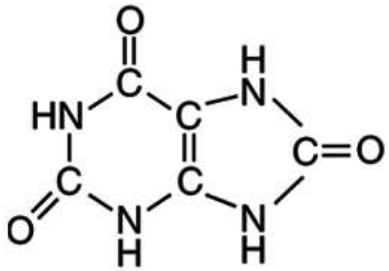
- **Remove waste products from the blood such as urea and creatinine**
- **Control the acid base balance (through HCO_3^- & H^+)**
- **Electrolyte homeostasis (K^+, Na^+ and Ca^{++})**
- **Secrete Hormones and enzyme like erythropoietin and rennin. CRF leads to anemia**
- **Activates Vitamin D.**
- **Regulate body fluids and arterial blood pressure**
- **Make G from non CHO sources (make sugar from proteins at time of starvation (gluconeogenesis).)**

Nitrogenous Wastes

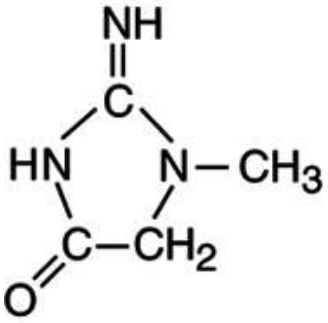
- Urea
  - proteins→ amino acids →NH_2 removed → forms ammonia, liver converts it to urea
- Uric acid
  - nucleic acid catabolism
- Creatinine
  - creatinine phosphate catabolism…muscle proteins…the more the muscle mass…the more the creatinine
- Renal failure
  - azotemia: accumulation of nitrogenous wastes in blood
  - uremia: toxic effects as wastes accumulate



Urea



Uric acid



Creatinine

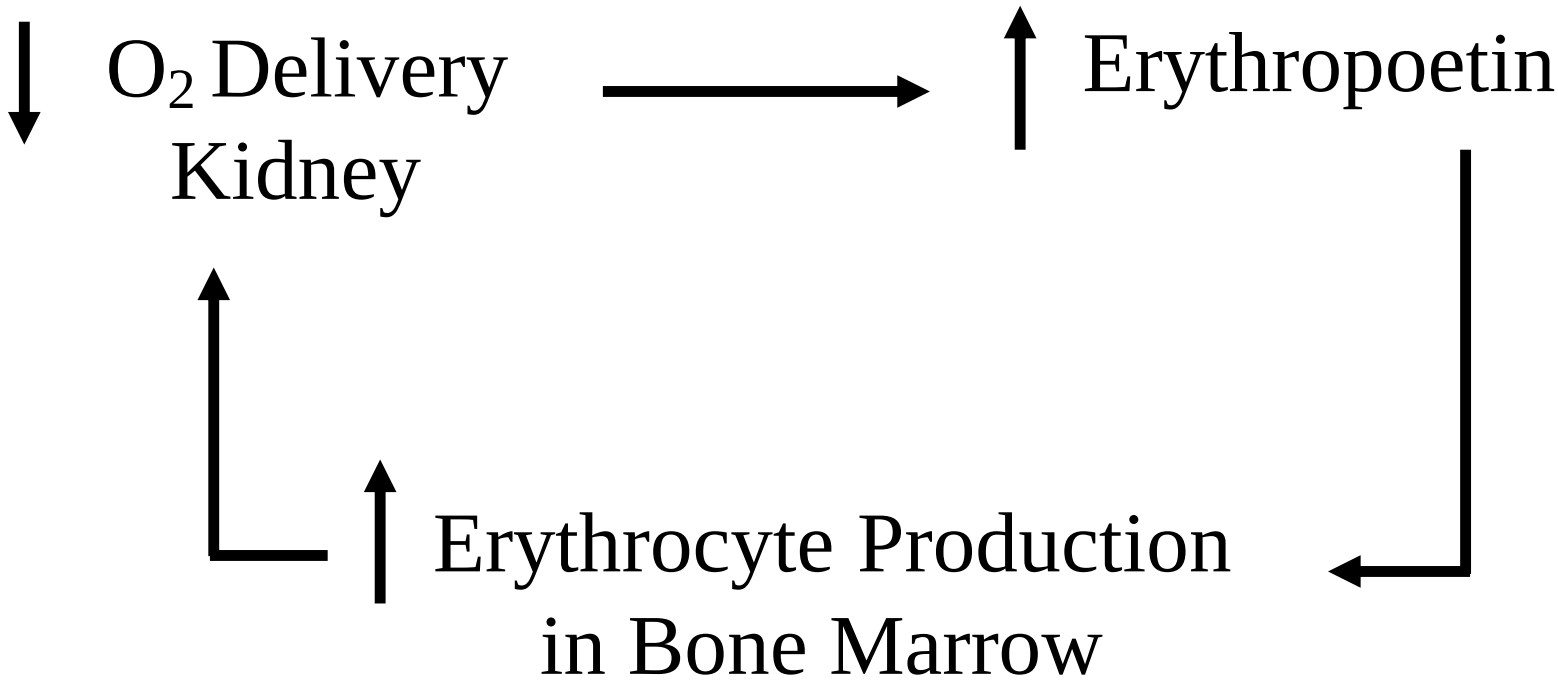
Excretion of Metabolic Waste Products

- Urea (from protein metabolism)
- Uric acid (from nucleic acid metabolism)
- Creatinine (from muscle metabolism)
- Bilirubin (from hemoglobin metabolism)

Excretion of Foreign Chemicals

- Pesticides
- Food additives
- Toxins
- Drugs…drug dose correction

Regulation of Erythrocyte Production



Regulation of Vitamin D Activity

- Kidney produces active form of vitamin D (1,25 dihydroxy vitamin D_3)…renal failure…osteoporosis
- Vitamin D_3 is important in calcium and phosphate metabolism

Regulation of Acid-Base Balance

- Excretion of nonvolatile acids (kidneys are the only means of excreting non-volatile acids)… Regulate body fluid buffers (e.g. Bicarbonate) reabsorption of HCO3…making new HCO3

Glucose Synthesis

Gluconeogenesis: kidneys synthesize glucose from precursors (e.g., amino acids) during prolonged fasting…starvation

Regulation of Arterial Pressure

Endocrine Organ

- renin-angiotensin system
- prostaglandins
- kallikrein-kinin system

Control of Extracellular Fluid Volume

Regulation of Water and Electrolyte Balances

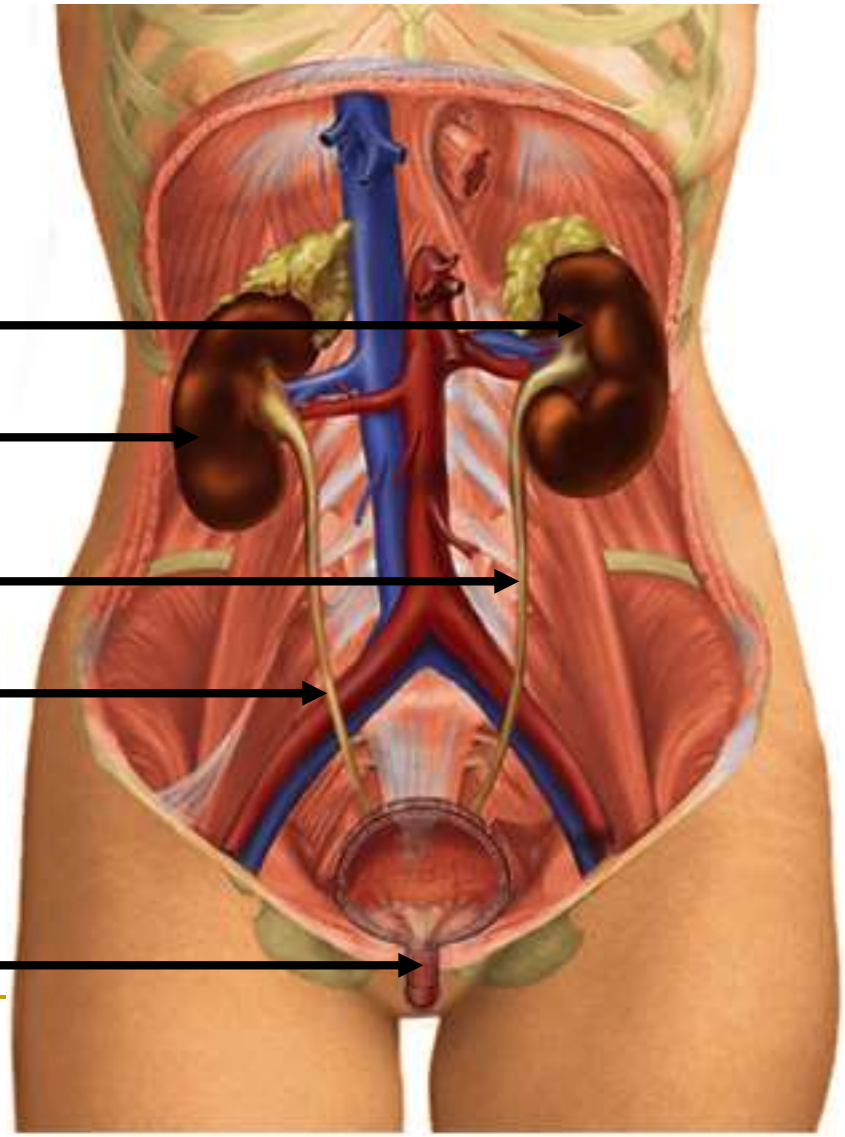
- Sodium and Water
- Potassium… very important
- Hydrogen Ions (pH)
- Calcium, Phosphate, Magnesium

Urinary System

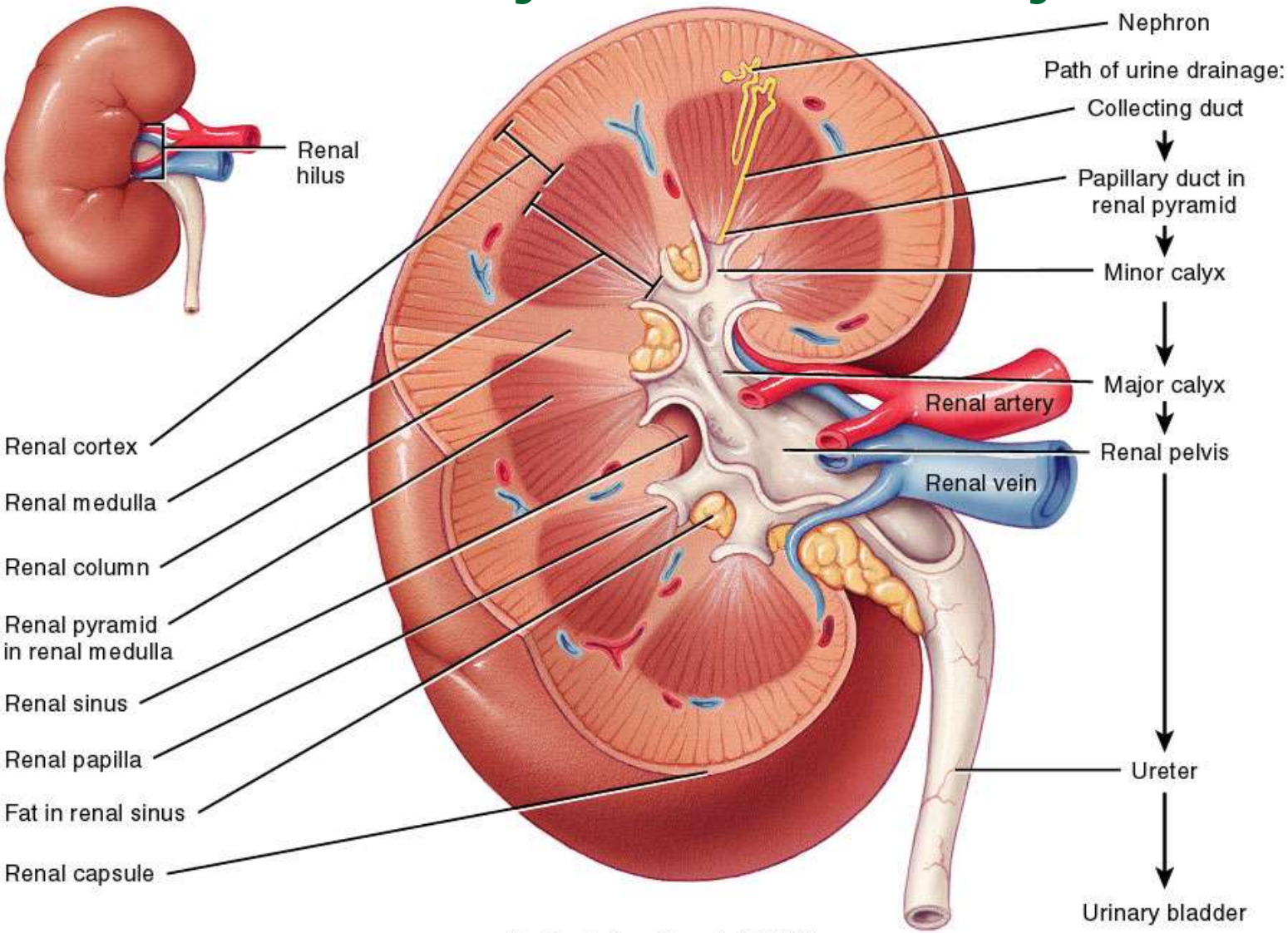
- Two kidneys

Two ureters

Urethra

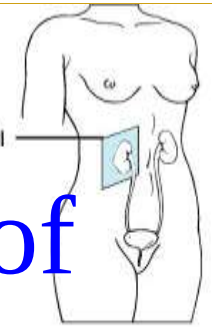


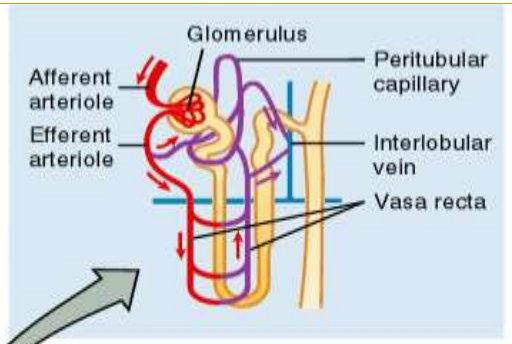
Internal anatomy of the kidneys



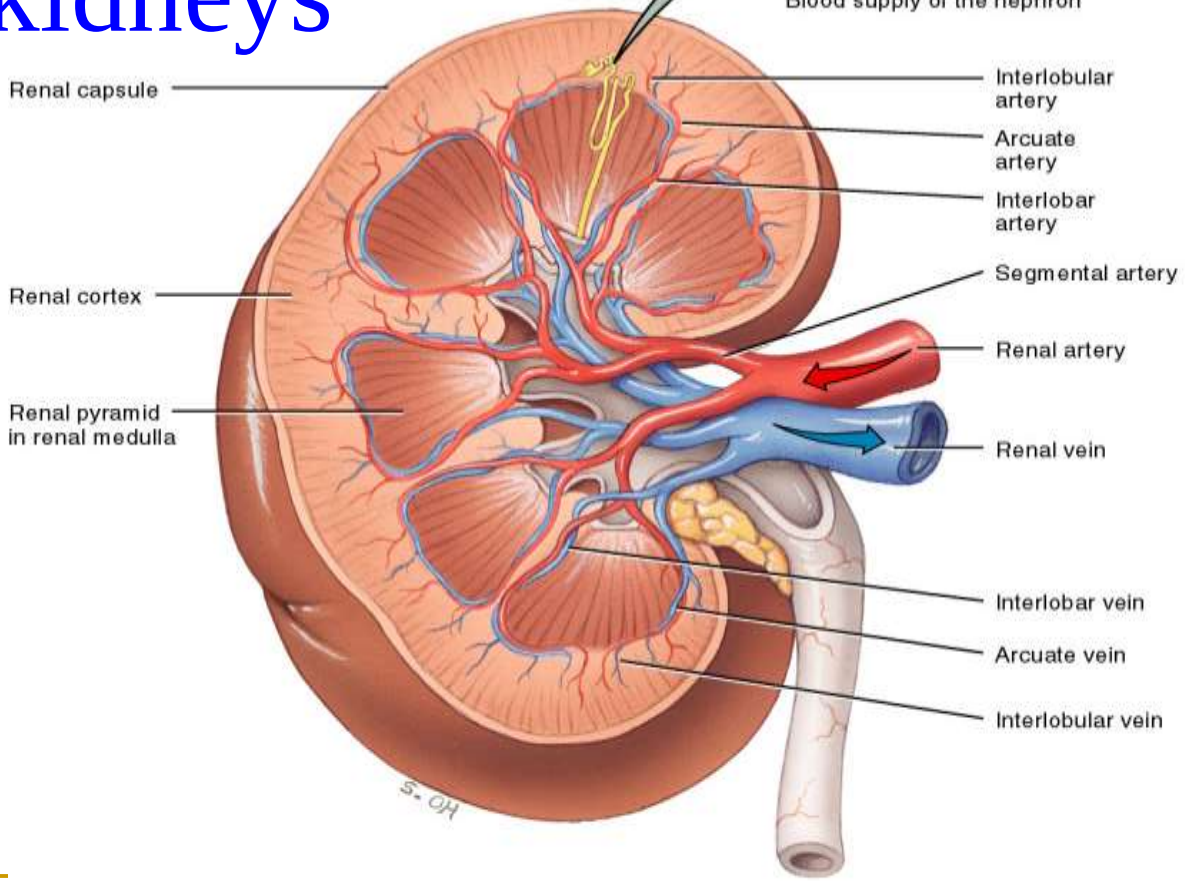
(a) Frontal section of right kidney

Blood supply of the kidneys

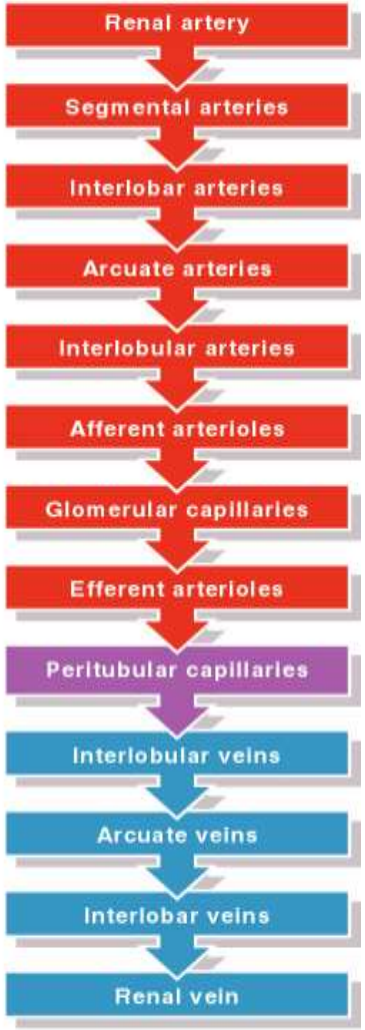




Blood supply of the nephron



(a) Frontal section of right kidney



(b) Path of blood flow

Functions of Nephron Structures

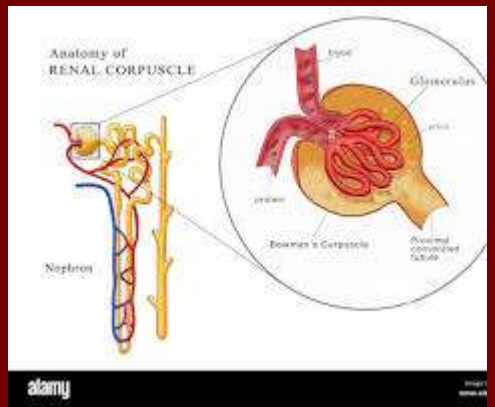
- **Afferent Arteriole**
  - **Transports arterial blood to the glomerulus for filtration**

Functions of Nephron Structures

- **Efferent Arteriole**
  - **Transports filtered blood from the glomerulus , through the peritubular capillaries and the vasa recta, and to the kidney venous system**

Functions of Nephron Structures

- **Glomerulus**
  - **The site for blood filtration**
  - **operates as a nonspecific filter; in that, it will filter both useful and non-useful material**
  - **the product of the glomerulus is called filtrate or ultrafiltrate**



Functions of Nephron Structures

- **Bowman's Capsule**
  - **A sac that encloses Bowman's Capsule and transfers filtrate from the glomerulus to the Proximal Convoluted Tubule (PCT)**

Functions of Nephron Structures

- **Proximal Convoluted Tubule (PCT)**
  - A thick, constantly actively segment of the nephron that reabsorbs most of the useful substances of the filtrate: sodium (65%), water (65%), bicarbonate (90%), chloride (50%), glucose and a.a (nearly 100%!), etc.
  - The primary site for secretion (elimination) of drugs, waste and hydrogen ions

Functions of Nephron Structures

- **Descending Limb of the Loop of Henle**
  - A part of the counter current multiplier
  - freely permeable to water and relatively impermeable to solutes (salt particles)
  - receives filtrate from the PCT, allows water to be absorbed and sends "salty" filtrate on the next segment. "Saves water and passes the salt"

Functions of Nephron Structures

- **Ascending Limb of the Loop of Henle**
  - part of the counter current multiplier
  - **impermeable to water** and **actively transports (reabsorbs) salt** (NaCl) to the interstitial fluid of the pyramids in the medulla. "**Saves salt and passes the water.**"
  - the passing **filtrate becomes dilute** and the **interstitium becomes hyperosmotic**

Functions of Nephron Structures

- **Distal Convoluted Tubule (DCT)**
  - receives dilute fluid from the ascending limb of the Loop of Henle
  - **Variably active** portion of the nephron
  - When **aldosterone** hormone is present, **sodium is reabsorbed,** and **potassium is secreted.** Water and chloride follow the sodium.

Functions of Nephron Structures

- **Collecting Duct**
  - receives fluid from the DCT
  - variably active portion of the Nephron
  - when antidiuretic hormone (ADH) is present, this duct will become porous to water. Water from the collecting duct fluid then moves by osmosis into the "salty" (hyperosmotic) interstitium of the medulla.
  - The last segment to save water for the body

Functions of Nephron Structures

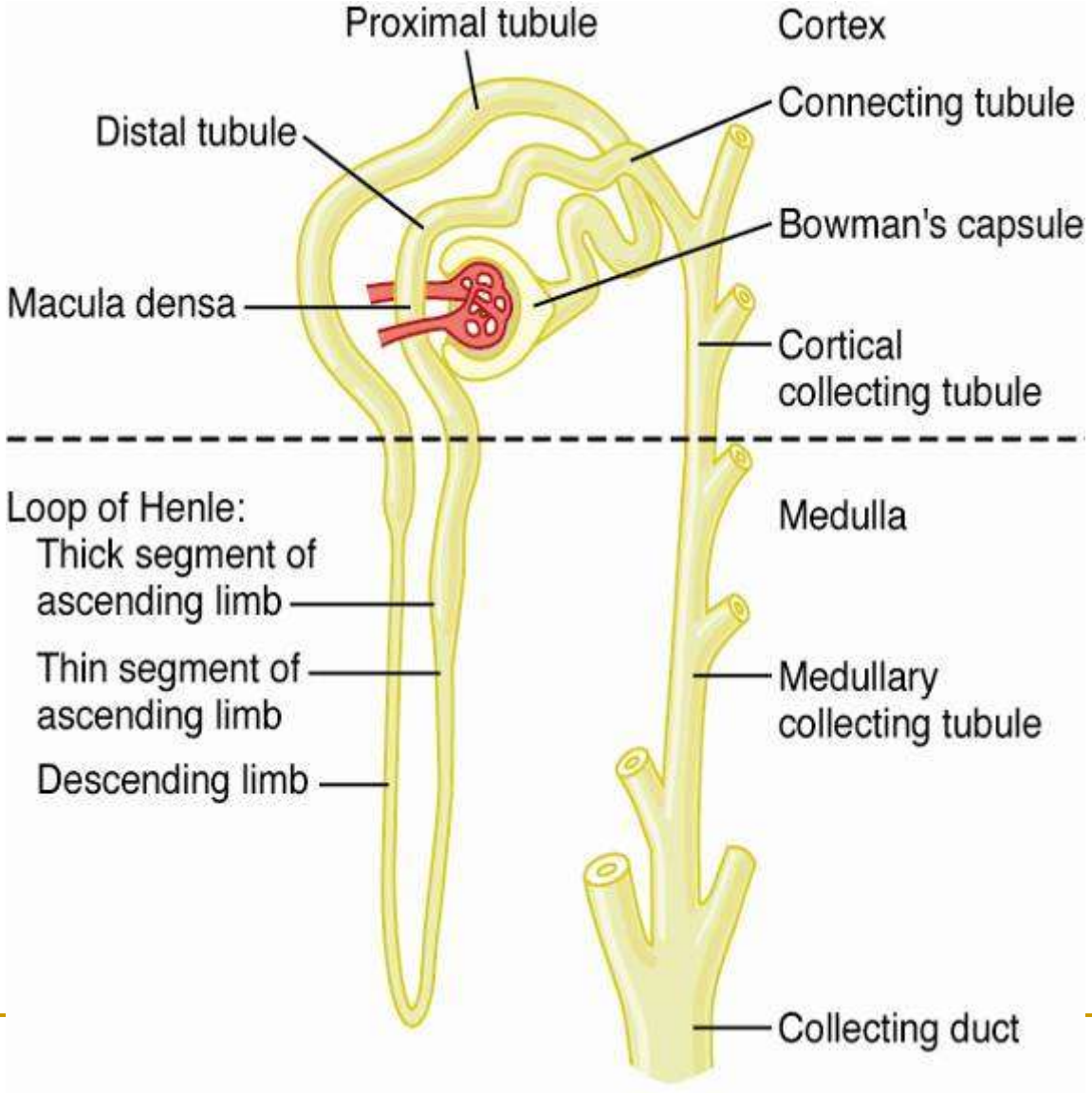
Peritubular Capillaries

- transport reabsorbed materials from the PCT and DCT into kidney veins and eventually back into the general circulation
- help complete the conservation process (reabsorption) that takes place in the kidney

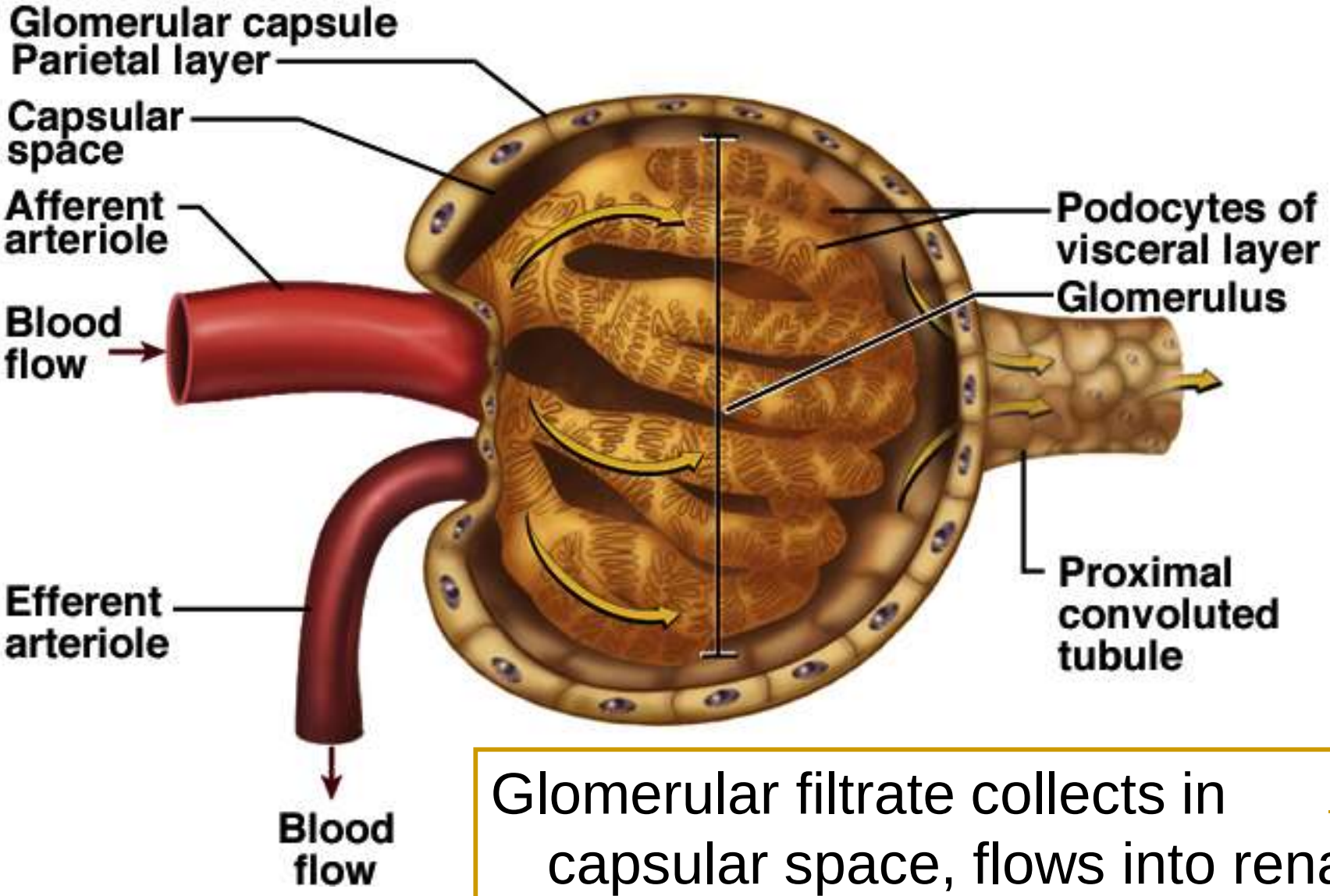
Slide related more to anatomy

- The kidney weighs 113-170 gm.
- Renal artery arises as the fifth branch of the abdominal aorta. The renal artery arises from the aorta at the level of the second lumber vertebra. Because the aorta is to the left of the midline, the right renal artery is longer. The inferior vena cava lies to the right midline making the left renal vein two times longer than the right renal vein. For this reason, it is better to take the donor left kidney (short artery, long vein) & place it in the right pelvis of the recipient. Multiple arteries & veins can supply the kidney.

Nephron Tubular Segments

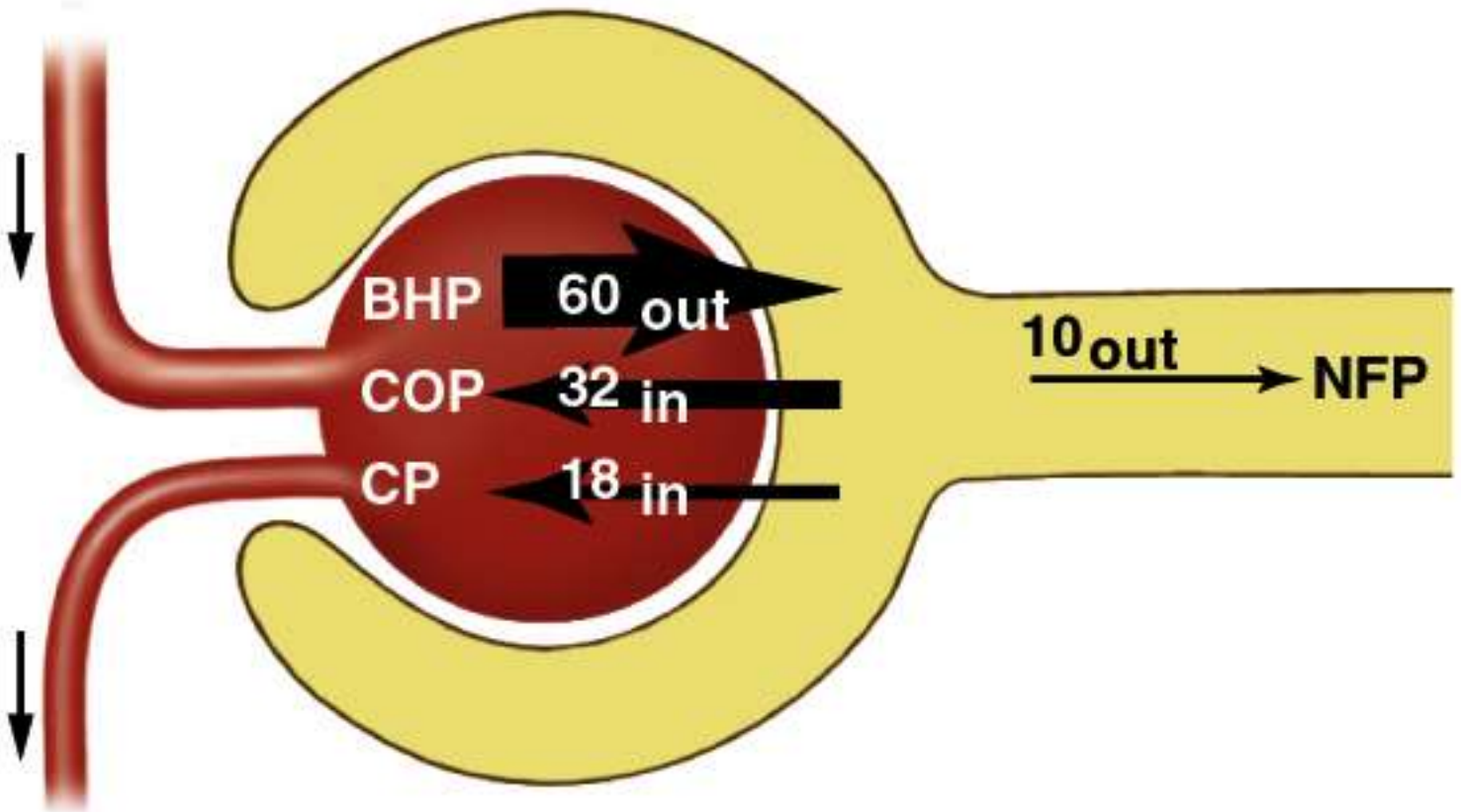


Renal Corpuscle



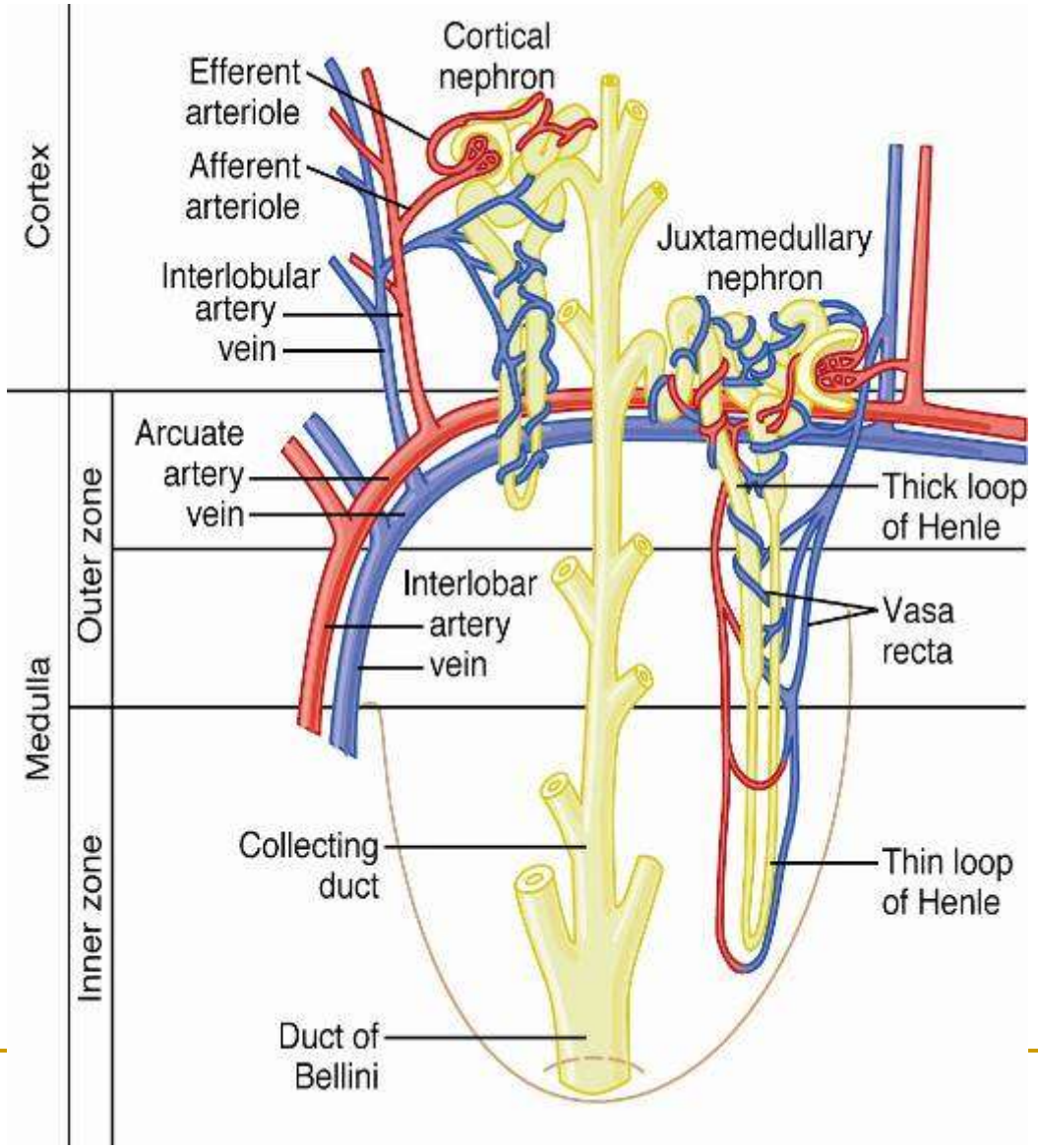
Glomerular filtrate collects in capsular space, flows into renal

Filtration Pressure…Starlin Forces are 3, not 4



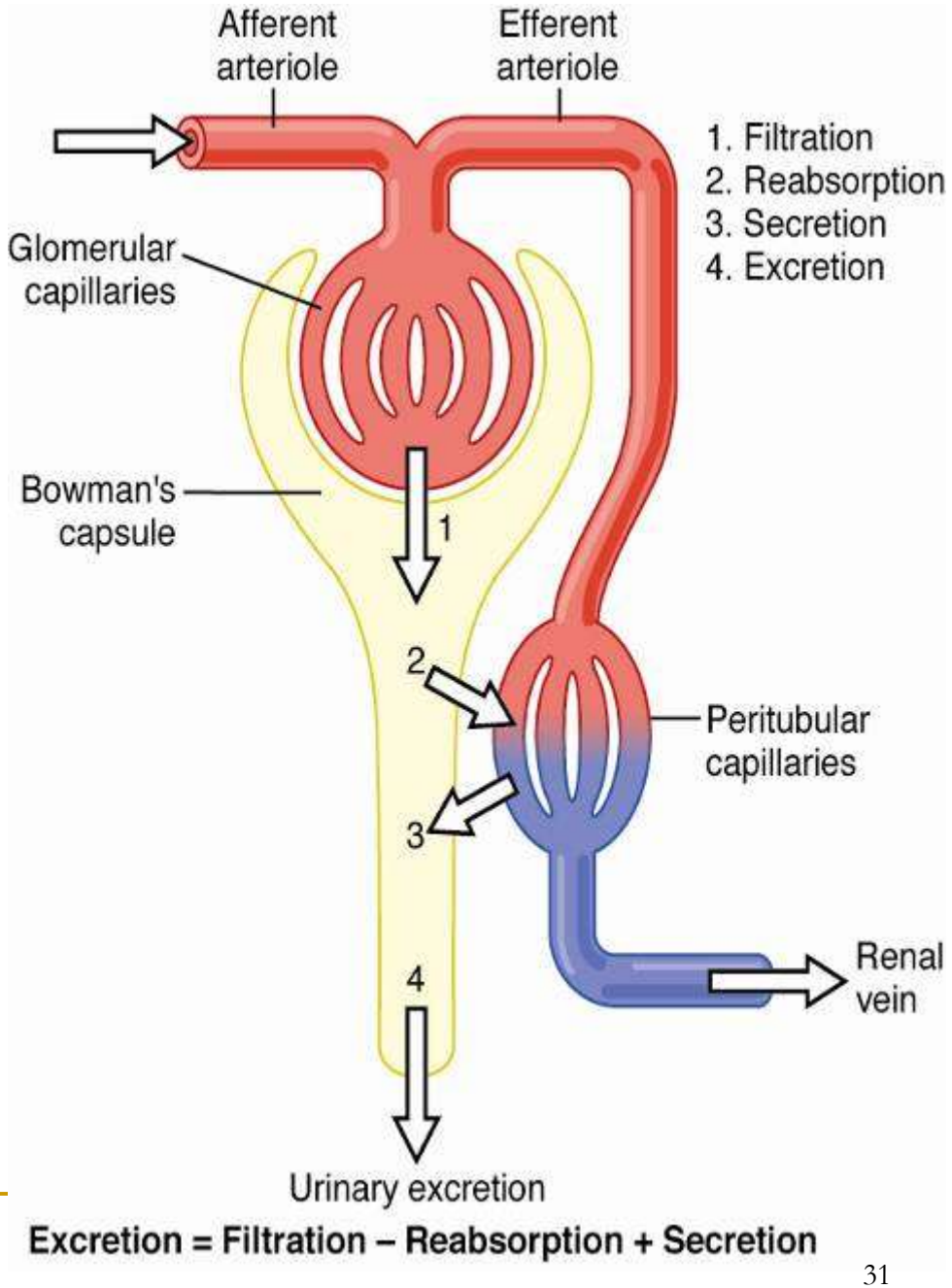
Blood hydrostatic pressure (BHP)	60 mmHg out
Colloid osmotic pressure (COP)	–32 mmHg in
Capsular pressure (CP)	–18 mmHg in
Net filtration pressure (NFP)	10 mmHg ou

Cortical and juxtamedullary nephrons

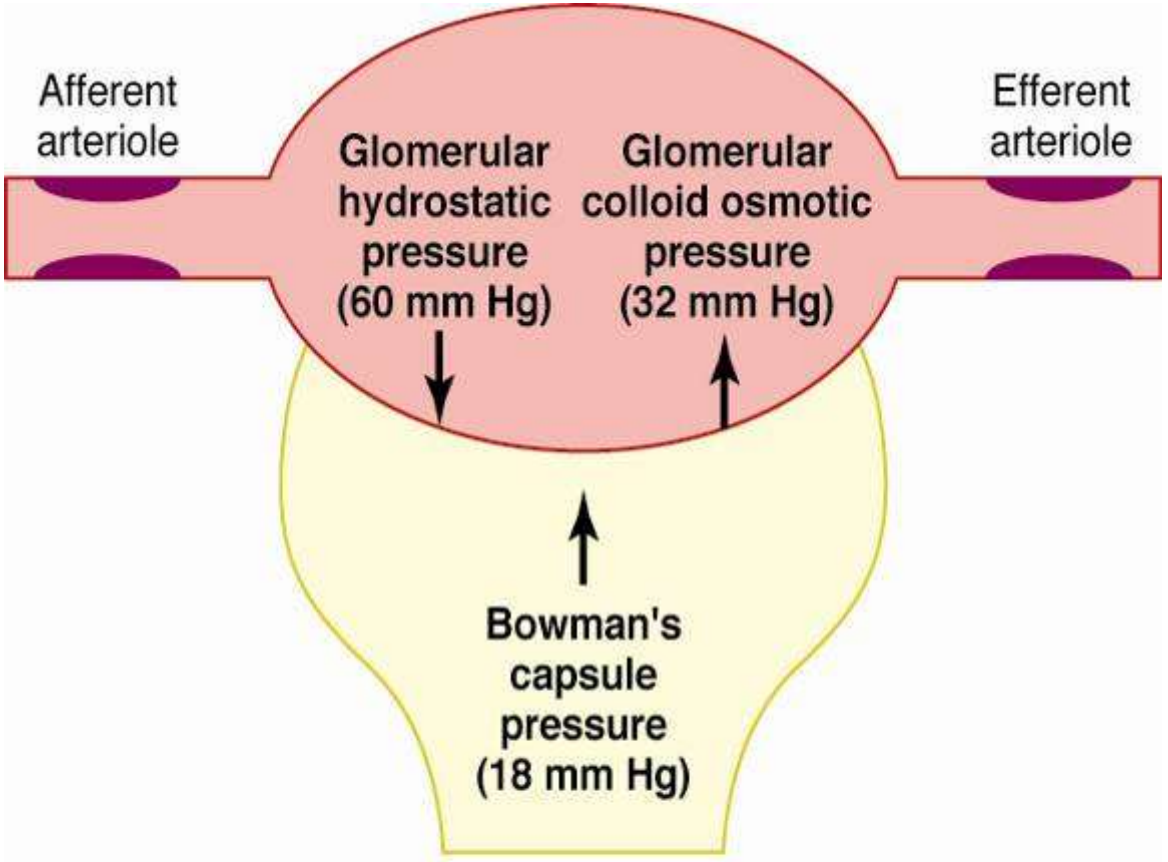


Basic Mechanisms of Urine Formation

renal filtrate or tubular fluid is precursor to urine

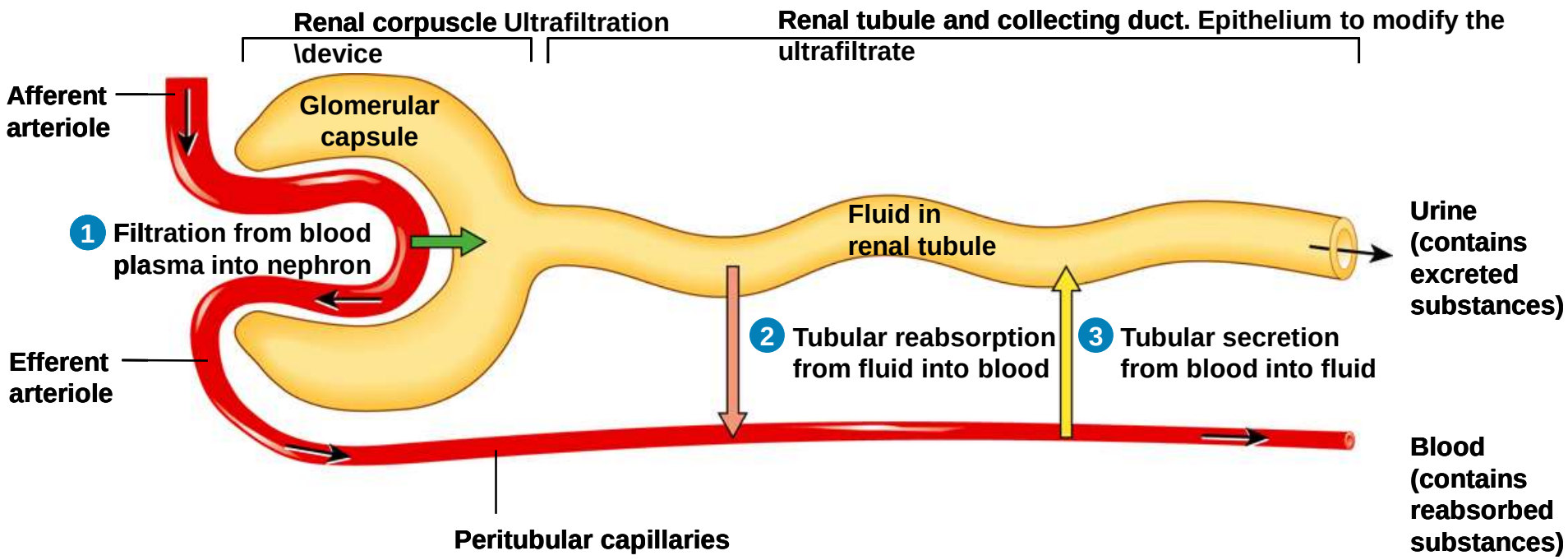


Determinants of Glomerular Filtration Rate



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)

Structures and functions of a nephron



Oversimplification of Functional Anatomy of the Kidneys

- Structure & function of the kidney are closely matched. The kidney is a combination of:

1. Ultrafiltration device (the glomerular apparatus).
2. Epithelium (tubules), which will later modify this ultrafiltrate either by:
   - addition (secretion) or
   - removal (reabsorption).

- Filtration in kidney is also affected, as systemic capillaries, by the 4 Starling forces (Hydrostatic & Osmotic pressure in & out…4 forces…from your CVS system and the introduction to physiology in the first year).
- Bowman's capsule stands for the interstitium
- To be discussed with regulation of GFR

RBF

- Remember from the respiratory system: Kidneys are reconditioning organs i.e. Receive too much blood. RBF= 20-25% of Q →→ This makes the A-V oxygen difference small (1.4 ml/dl). Look at the next slide.
- Nevertheless, kidneys consume twice O_2/per gm tissue as brain.
- This O_2 consumption is directly related to Na^+ reabsorption (extremely important clinical point). If GFR is high → Na^+ reabsorption is high→O_2 consumption is high. When GFR is severely depressed (AKI) → decreased need for O_2 ….nothing to reabsorb
- If RBF decreases →→ acute kidney injury.
-

Blood Flow to Different Organs

Tissue	Blood flow (ml/g/min)	[A-V O_2] difference (Vol %)	Flow ml/min	O_2 consumption ml/min
Heart	0.8	11	250	27
Brain	0.5	6.2 (25-30% Extraction)	750-900	
Skeletal Muscle	0.03	6	1200	70
Liver	0.6	3.4 Preconditioner organ		
SKIN	0.1			
Kidney	4.2	1.4 Preconditioner organ	1250	18
Carotid bodies	20	0.5 Preconditioner organ	0.6	

Renal Function

- Renal Plasma Flow = ~650 cc / min total

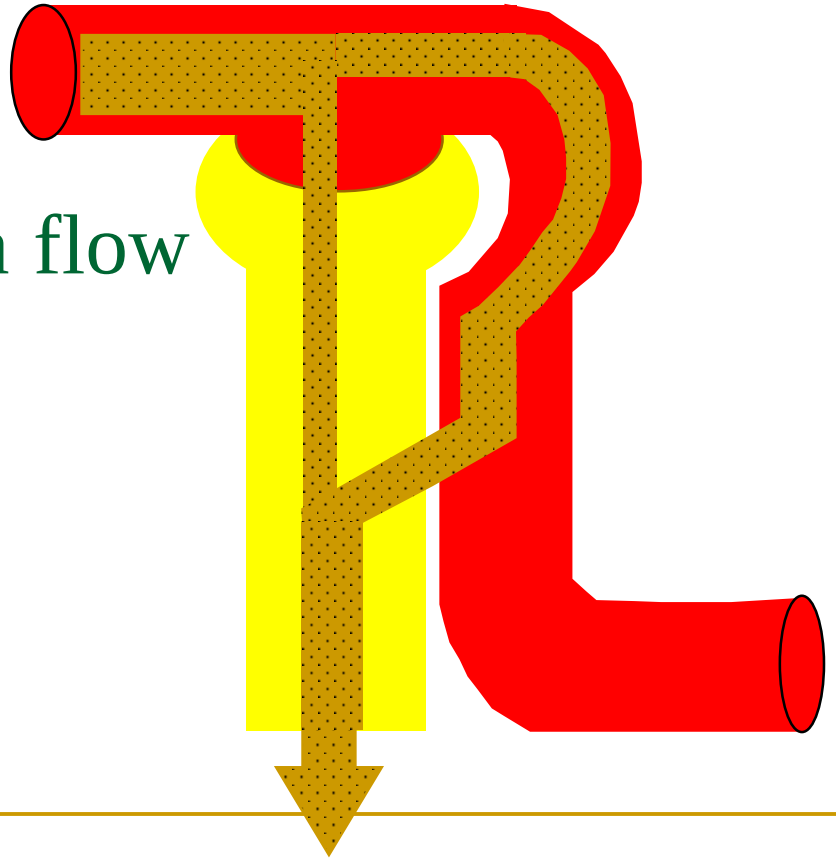
- Renal Cortex = ~500 cc / min
- Outer Medulla = ~125 cc / min
- Inner Medulla = ~25 cc / min

How to measure Renal Plasma Flow (RPF) Briefly:

- RPF : how much plasma enter both kidneys per minute.
- We use a substance X that is completely removed (cleaned) from the blood once it reaches the kidneys: i.e. Renal vein concentration of X = 0
- i.e; once comes to the peritubular capillaries is completely secreted.
- The substance used commonly here is the PAH (para-aminohippuric acid.)

Theoretically, if a substance is completely cleared from the plasma, its clearance rate would equal renal plasma flow

Cx = renal plasma flow



Use of PAH Clearance to Estimate Renal Plasma Flow

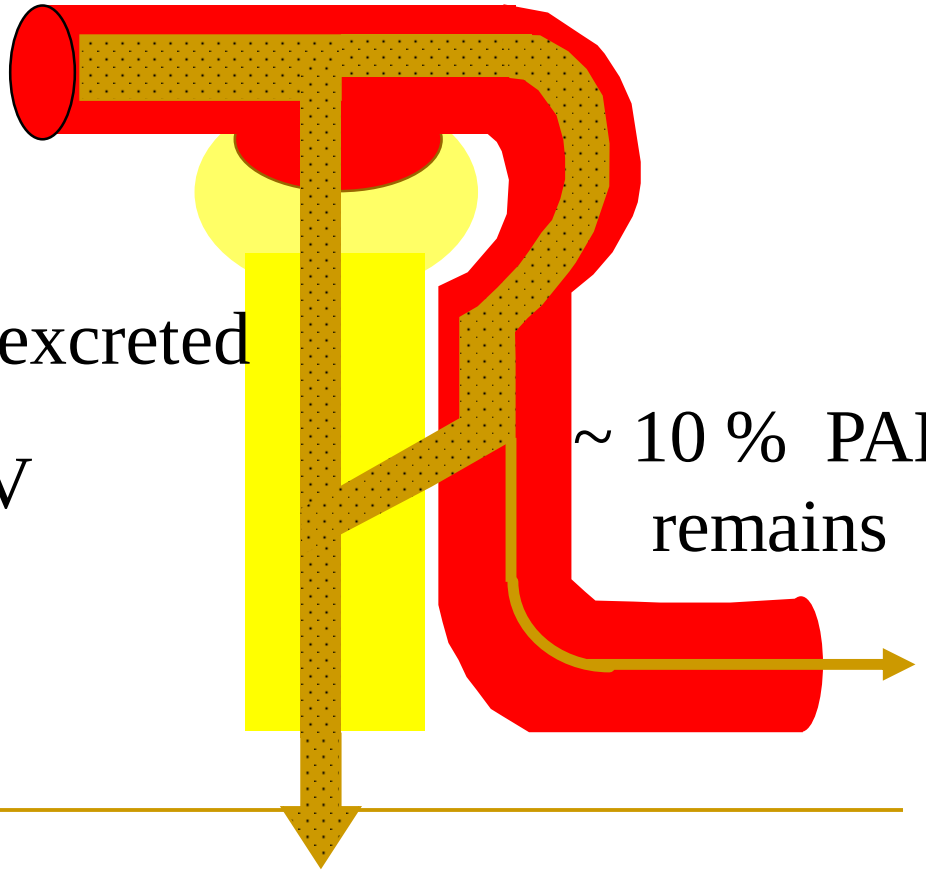
Paraminohippuric acid (PAH) is freely filtered and completely secreted and thus is almost completely cleared from the renal plasma

1. amount enter kidney =
   RPF x P_{PAH}

2. amount entered ≈ amount excreted

3. ERPF x P_{PAH} = U_{PAH} x V

$$ERPF = \frac{U_{PAH} \times V}{P_{PAH}}$$



ERPF = Clearance PAH

To calculate actual RPF , one must correct for incomplete extraction of PAH

$A_{PAH} = 1.0$

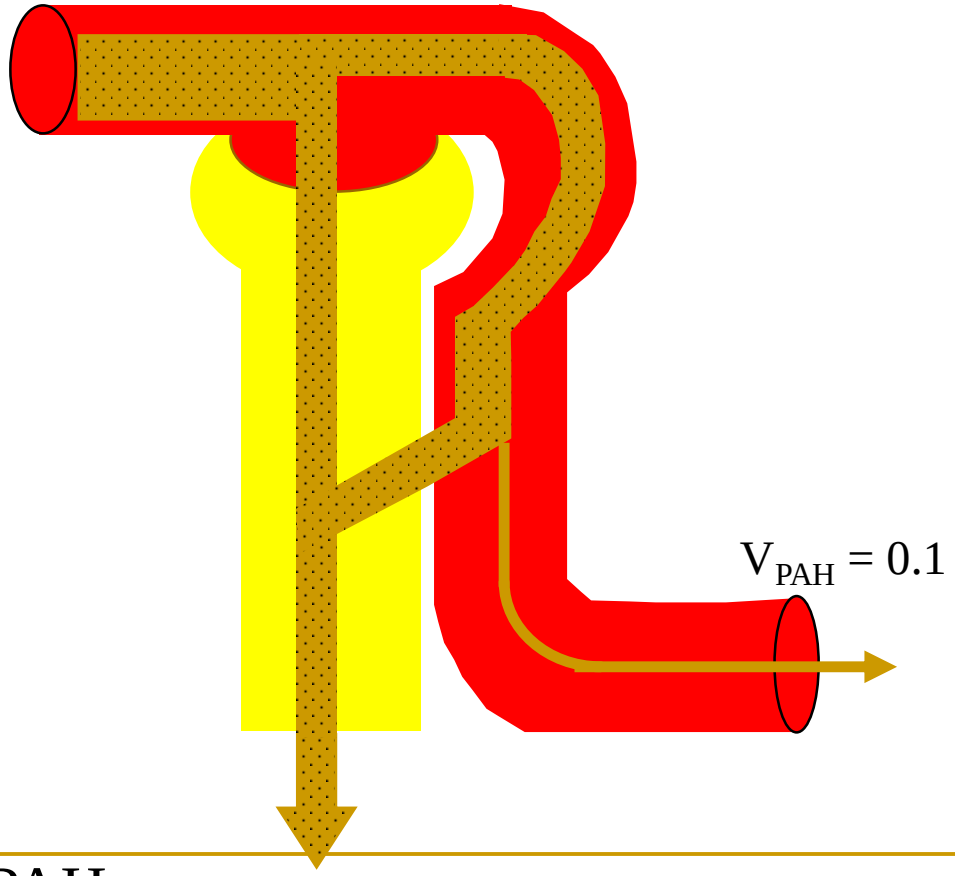
$$E_{PAH} = \frac{A_{PAH} - V_{PAH}}{A_{PAH}}$$

$$= \frac{1.0 - 0.1}{1.0} = 0.9$$

normally, $E_{PAH} = 0.9$

i.e PAH is 90 % extracted

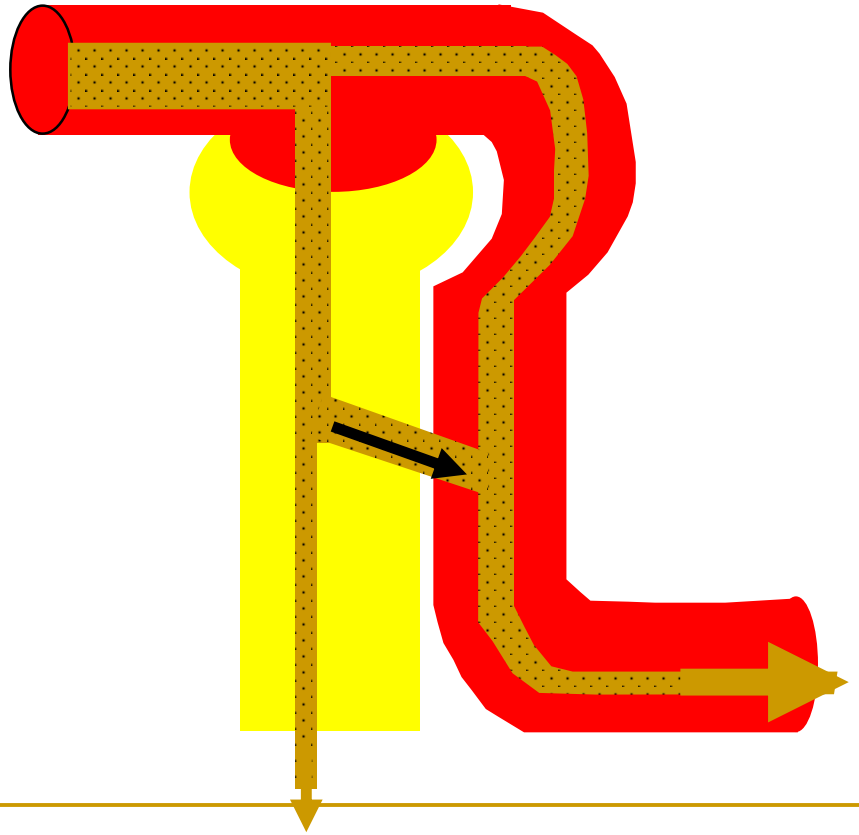
$$tRPF = \frac{ERPF}{\text{Extraction of PAH}}$$



Calculation of Tubular Reabsorption

Reabsorption = Filtration -Excretion

Filt s = GFR x Ps



Excret s = Us x V

Question

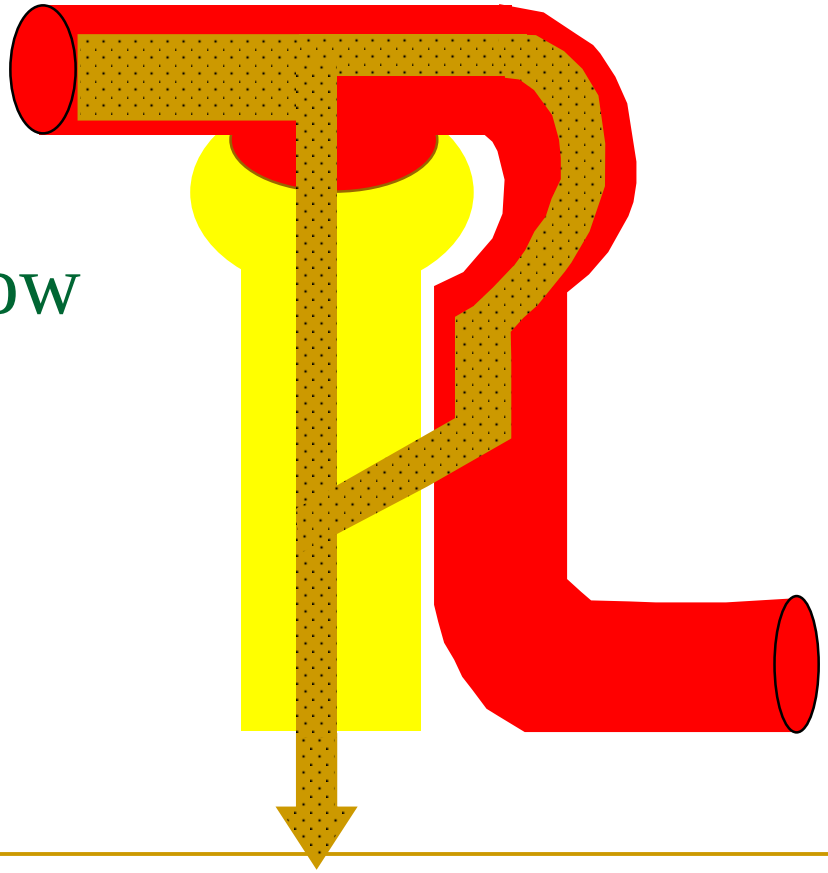
Question: The maximum possible clearance rate of a substance that is completely cleared from the plasma by the kidneys would be equal to

1. glomerular filtration rate
2. the filtered load of the substance
3. urine excretion rate of the substance
4. renal plasma flow
5. Renal blood flow

Use of Clearance to Estimate Renal Plasma Flow

Theoretically, if a substance is completely cleared from the plasma, its clearance rate would equal renal plasma flow

Cx = renal plasma flow



Clearances of Different Substances

Substance	Clearance (ml/min)
inulin	125
PAH	585
glucose	0
sodium	0.9
urea	70

Clearance of inulin (C_{in}) = GFR

if Cx < Cin : indicates reabsorption of x

if Cx > Cin : indicates secretion of x

Clearance creatinine (C_{creat}) ~ 140 (used to estimate GFR)

Clearance of PAH (C_{PAH}) ~ effective renal plasma flow

Measurement of RPF (Not a routine clinical test..but you might receive a question in USMLE part I):

$$Cx = \left[\frac{U_x}{P_x}\right] * V$$

C_{PAH} underestimate the tRPF. The C_{PAH} is the effective RPF. The true RPF is 10% higher. 10% of RBF goes to the medulla, hilum, pelvis and does not participate in renal function…etc.

p-aminohippuric acid PAH is an exogenous organic anion and not produced in our body.
Freely filtered, not reabsorbed, completely secreted. In the kidney it is not metabolized, accumulated, or produced.
Tm = 80 mg/min

Extraction ratio of PAH MW=194

$$Extraction E_{PAH} = \left[\frac{A_{PAH} - V_{PAH}}{A_{PAH}}\right] * 100\%$$

$$RPF = \left[\frac{U_{PAH}}{P_{PAH}}\right] * V$$

$$tRPF = \left[\frac{effRPF}{0.9}\right]$$

$$RBF = \left[\frac{RPF}{1 - Hct}\right]$$

RPF

- 650 ml is the RPF.
- 125 is filtered (GFR).
- How much is the filtration fraction?...≈ 20%
- 525 leave through efferent arteriole and go to peritubular capillaries.
- 1 ml/min is the urine output.
- Renal artery brings 650 ml/min while Renal vein carries 649 ml/min

Example

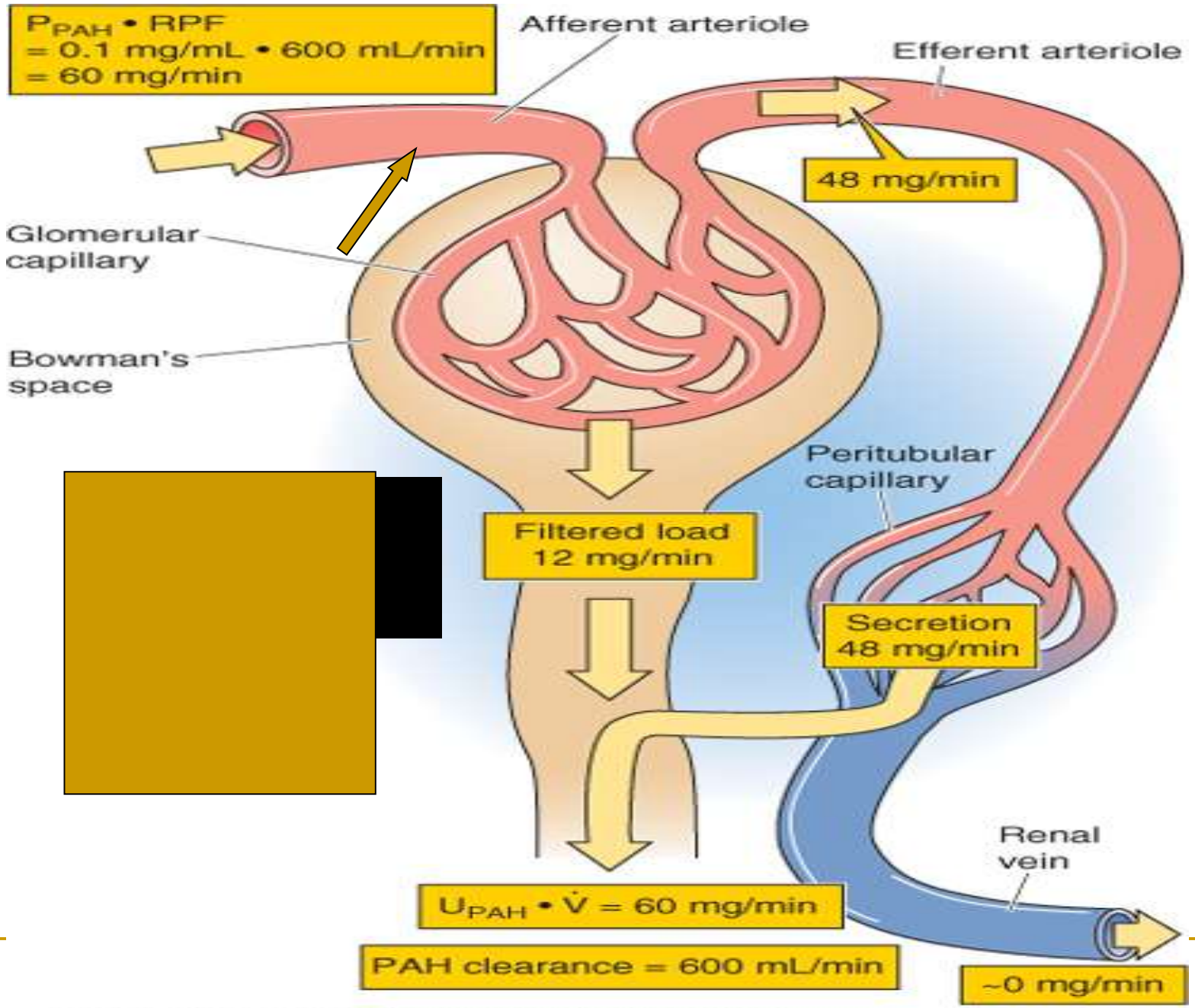
- NOTE : as said before..RPF is **not** a routine clinical test.
- So.. if we inject a certain amount of PAH in blood to achieve certain blood concentration.
- If RPF is 650ml/min.
- And urine output is 1 ml/min
- Then, the concentration of PAH will increase 650 times in the urine.
- But actually, this is not the case. Because 10 % of renal blood goes to nourish the kidney i.e. don’t participate in the renal function….don't reach the glomeruli from the beginning
- So 585 ml/min (90%) is the effective RPF and 650 ml/min (100%) is called true or total RPF.
- True RBF = effective RBF ÷ 0.9 .

PAH CURVE for FILTRATION and SECRETION :

- Remember: Filtration is passive.
- Secretion is active (shows saturation and Tmax).
- Filtered load of “x” : is how much of “x” is being filtered/minute.
- Filtered load is proportional to its plasma conc. (linear)…no plateau.no Tmax
- Since GFR = 125……filtration counts for 125/650 = 20 % of excretion of PAH in urine.
- Secretion counts for 80 %.
- Secretion exhibit Tmax; (Transport maximum.)
- The excretion curve is the sum of both.

The source of PAH in the urine:

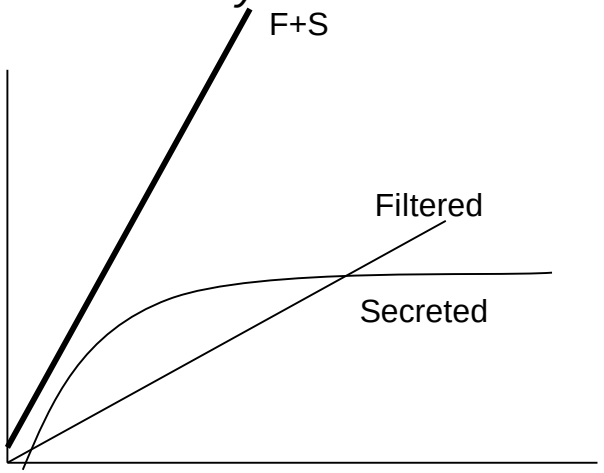
1. **filtration 20%**
2. **secretion 80%**
3. **without any reabsorption.**



Remember:

PAH must be completely cleared (or cleaned) from plasma in the kidney…

But only under one condition…name it……



- When we increase the PAH in the plasma, the filtration will increase proportionally (because filtration is a passive process).
(remember: 20% of the PAH is filtered)

- But in the case of secretion (which is an active process) after reaching Tmax…. No more increase in secretion…plateau phase

- So at a certain concentration the kidney will not be able to clear the whole plasma from that substance (Cr).

- If PAH delivered to the peritubular capillaries exceeds Tmax (80 mg/min) →→ PAH clearance becomes less than RPF (underestimation of RPF)

Let us look at it from different angle:
We will use "Law of Conservation of Mass":
Amount excreted in the urine/min = Amount provided for excretion (by artery)/min

- A x: is the amount of X entering the kidneys through the renal artery
- Ux: is the amount of X leaving the kidneys through urine

- "X" leaves the kidney through 1. renal vein or 2. through urine

Thus: Ax = Vx (we consider this portion equals zero) + Ux

• *Conditions must be met before using "x" as RPF marker: "X" does not accumulate, made, or catabolized by the kidney*

If we assume that Vx equals zero, then:

Ux = Ax

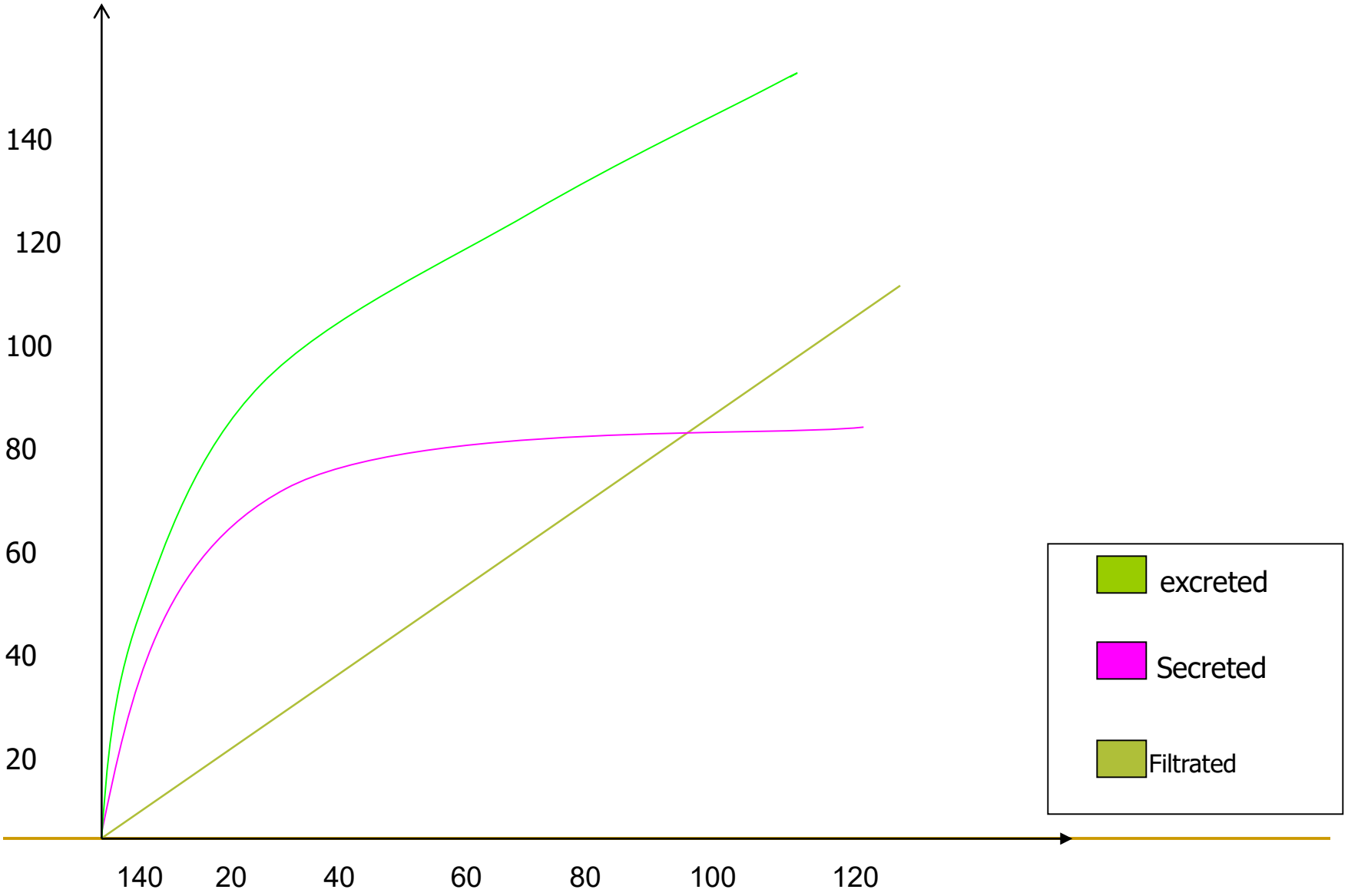
Amount Excreted of X (mg/min) = Urine output (V) * U_x

Amount provided for excretion (mg/min) = RPF * P_x P=plasma

So…

$$\mathbf{RPF = (U_x/P_x) * V}$$

PHA CURVE for FILTRATION and SECRETION :



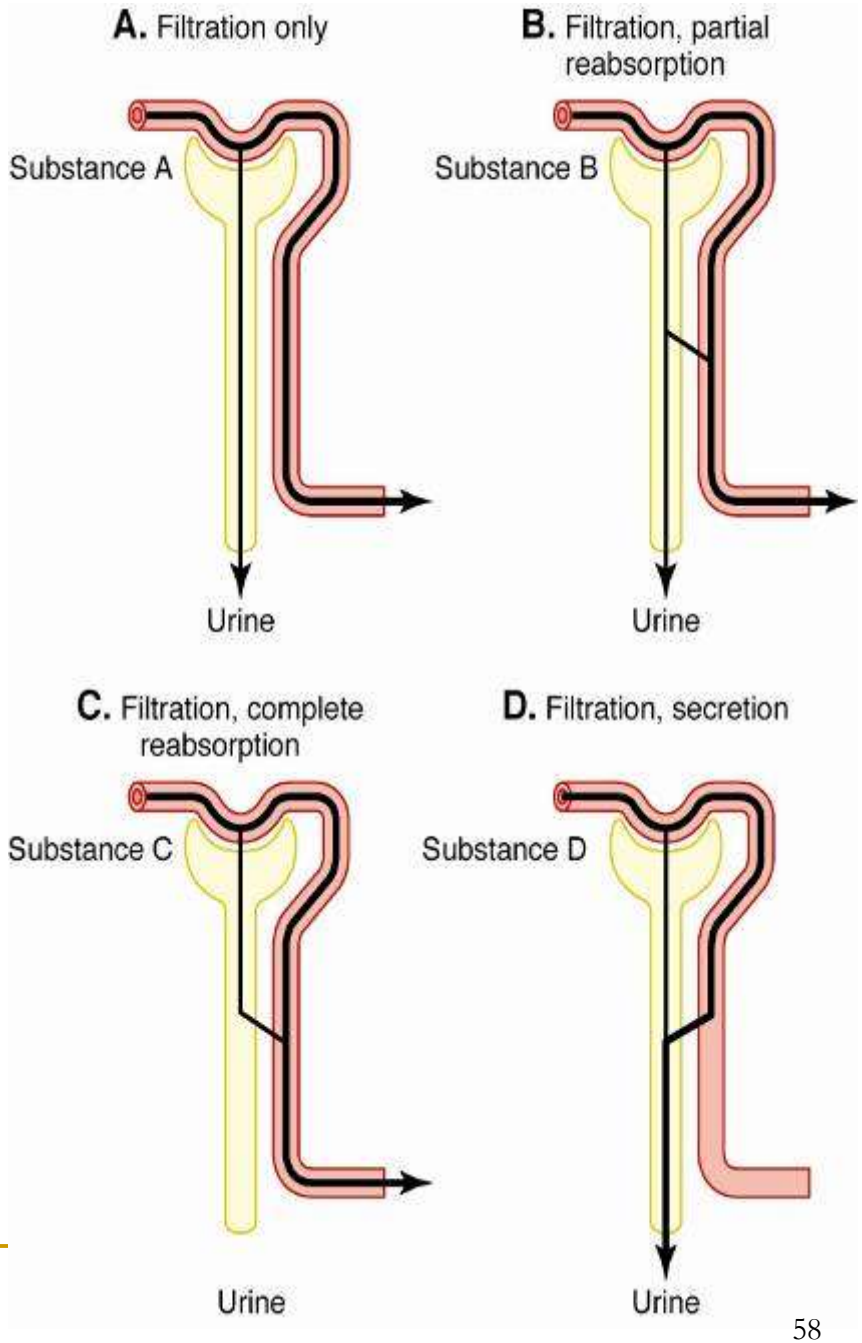
Excretion = Filtration - Reabsorption + Secretion

Filtration : somewhat variable, not selective (except for proteins), averages 20% of renal plasma flow

Reabsorption : highly variable and selective
most electrolytes (e.g. Na^+, K^+, Cl^-) and nutritional substances (e.g. glucose) are almost completely reabsorbed; most waste products (e.g. creatinine, urea) are not reabsorbed or poorly reabsorbed

Secretion : highly variable; important for rapidly excreting some waste products (e.g. $H^+$and K^+), foreign substances (including drugs), and toxins

Renal Handling of Different Substances



Renal Handling of Water and Solutes

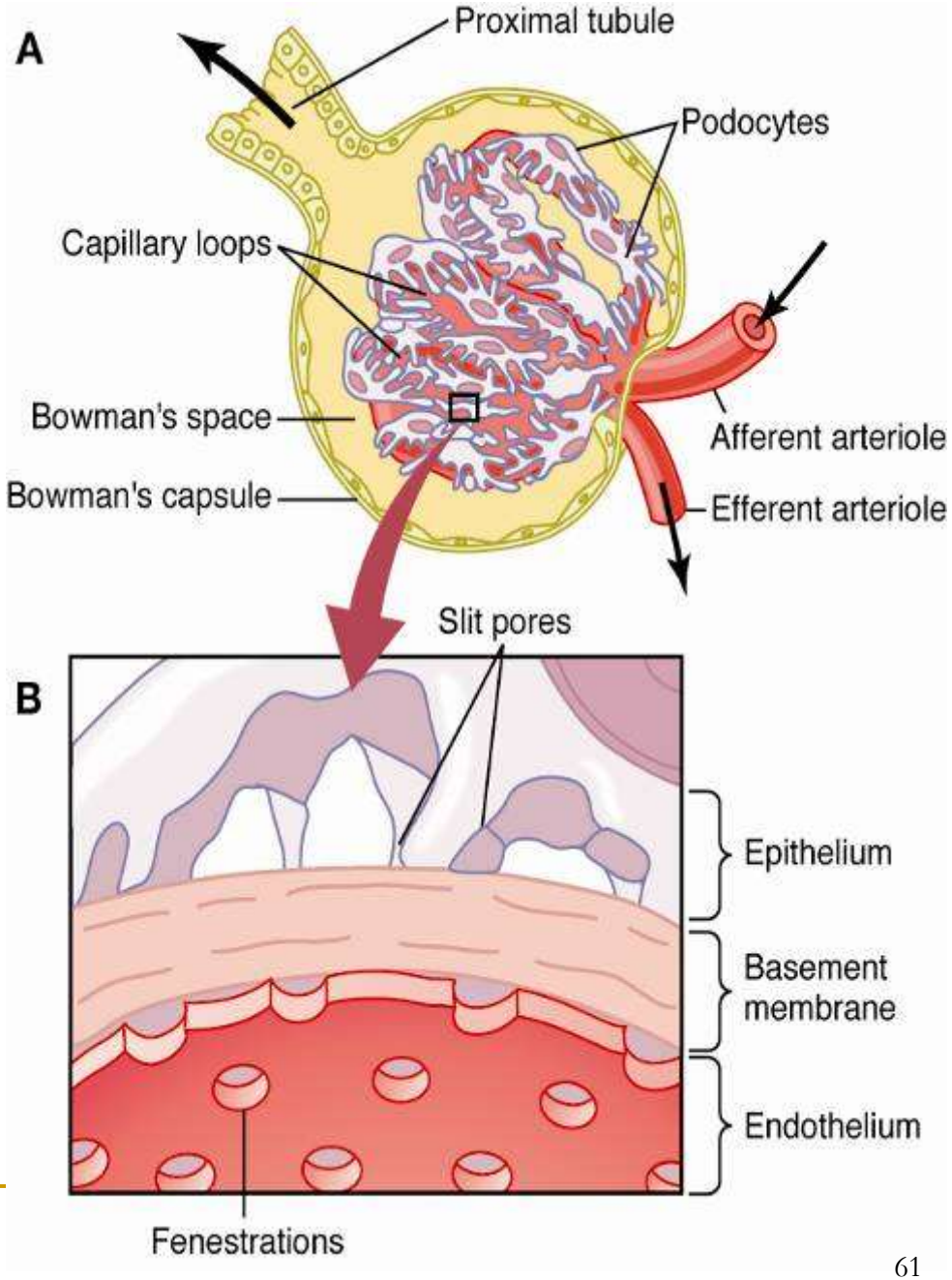
	Filtration	Reabsorption	Excretion
Water (liters/day)	180	178.5	1.5
Sodium (mmol/day)	25,560	25,410	150
Glucose (gm/day)	180	180	0
Creatinine (gm/day)	1.8	0	1.8

Glomerular Filtration

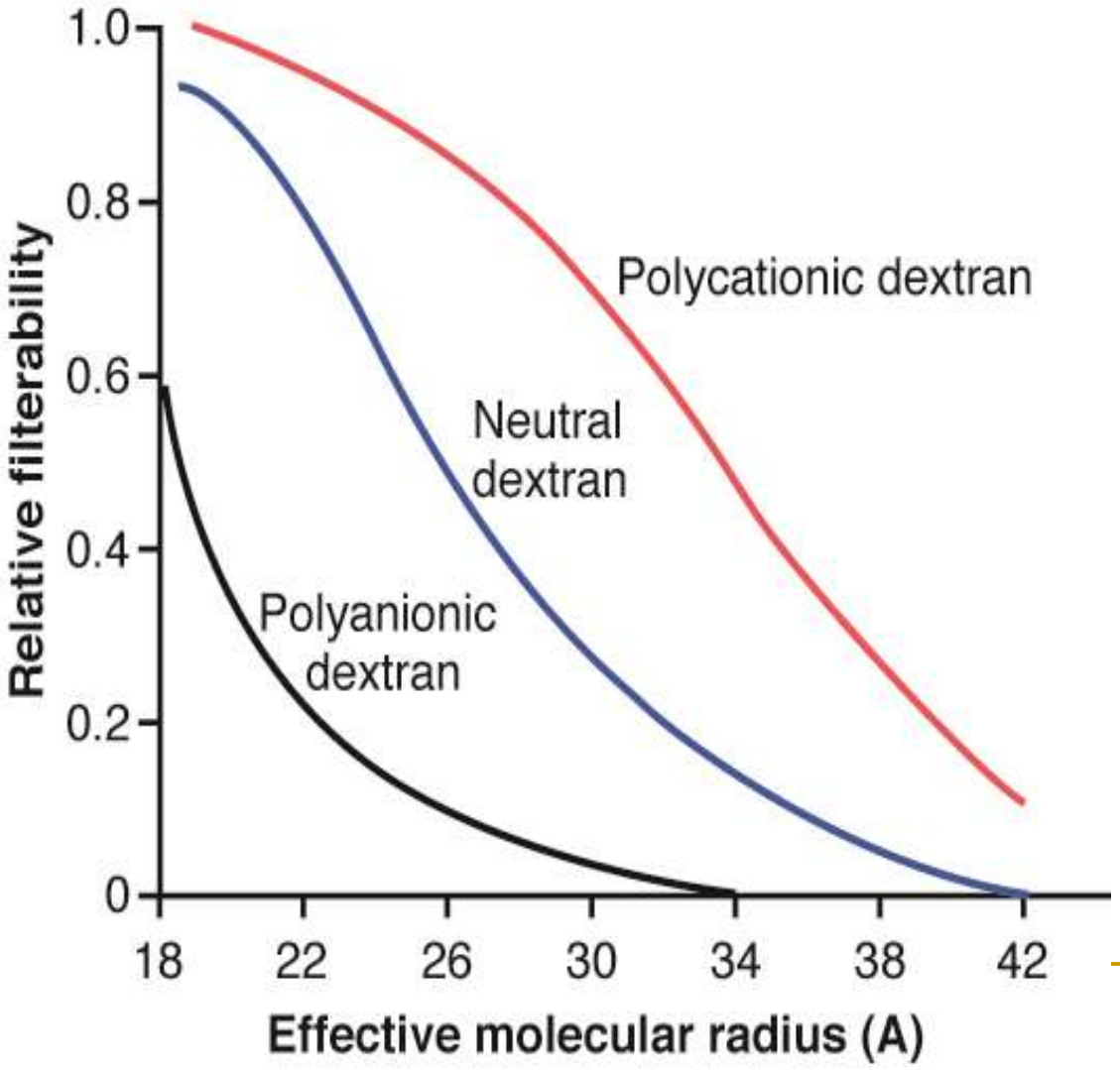
GFR = 125 ml/min = 180 liters/day

- Plasma volume is filtered 60 times per day
- Glomerular filtrate composition is about the same as plasma, except for large proteins
- Filtration fraction (GFR / Renal Plasma Flow) = 0.2 (i.e. 20% of plasma is filtered)

Glomerular capillary filtration barrier



Effects of size and electrical charge of dextran on filterability by glomerular capillaries.



Determinants of Glomerular Filtration Rate

Normal Values:

GFR = 125 ml/min

Net Filt. Press = 10 mmHg

K_f = 12.5 ml/min per mmHg, or

4.2 ml/min per mmHg/ 100gm

(400 times greater than in many other tissues)

Glomerular Capillary Filtration Coefficient (K_f)

- K_f = hydraulic conductivity x surface area. Cannot be measured directly
- Normally is <u>not</u> highly variable. 400 times as high as Kf of other tissues
- Disease that can reduce K_f and GFR
  - chronic hypertension
  - obesity / diabetes mellitus increases the thickness of the basement membrane
  - glomerulonephritis

Age	GFR/1.73 m^2	
	Males	Females
20-29	94-140	72-110
30-39	59-137	71-121
40-49	76-120	50-102
50-59	67-109	50-102
60-69	54-98	45-75
70-79	49-79	37-61
80-89	30-60	27-55
90-99	26-44	26-42

- ***Use of GFR to classify renal impairment***
- **1. Decreased Renal reserve. When 50% of the nephrons are destroyed (One kidney). GFR drops to 50%. Homeostasis is perfectly maintained. Urea and creatinine can be within the normal range.**
- **2. Renal Insufficiency: When GFR drops to 20-50%. The earliest sings is isosthenuria or polyuria with isotonic urine. Azotemia, anemia, and hypertension appear too.**
- **3. Renal Failure: GFR drops to less than 20% N. All signs and symptoms of uremia (urine in the blood) are present.**
- **4. End-stage Renal Disease ESRD: Occurs when GFR drops to less than 5% N. At this stage, dialysis or transplantation are necessary for survival. Is an administrative term rather than medical term. It means that person should be covered by government insurance, because replacement therapy is mandatory.**

$C_{creatinine}$…instead of inulin we use creatinine… we either use tGFR or eGFR ("t" stands for true and "e" stands for estimated

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

- **GFR = [(140-age in yr) X (weight in kg)]/(72 X serum creatinine in mg/dl).**
- Values for women are 85% of the predicted.
- The Modification of Diet in Renal Disease (MDRD):
- MDRD: 186 (serum creatinine in mg/dL)$^{-1.154}$ (age in years)$^{-0.203}$
- **Schwartz Formula in Children**
- GFR (mL/min/1.73 m^2) = k * Height (cm) / Serum Creatinine (mg/dl)
- k = Constant.
- k = 0.33 in premature Infants
- k = 0.45 in Term infants to 1 year old
- k = 0.55 in Children to 13 years
- k = 0.65 in Adolescent males….in females it remains 0.55

Modification of Diet in Renal Disease Formula (MDRD)

- The most recently advocated formula for calculating the GFR
- Etimates GFR using four variables:
  - Serum creatinine
  - Age
  - Race
  - Gender
- underestimates the GFR in healthy patients with GFRs over 60 mL/min
- Old : six variables ➔ albumin + BUN

- CKD ☺
- AKF ☹

$$186 \text{ (serum creatinine in mg/dL)}^{-1.154} \text{ (age in years)}^{-0.203}$$

Cockcroft-Gault formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

- Values for women are 85% of the predicted.
- Modification of Diet in Renal Disease (MDRD) equation
- 186 (serum creatinine in mg/dL)$^{-1.154}$ (age in years)$^{-0.203}$
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- k = 0.65 in Adolescent males….in females it remains 0.55

Chronic Kidney Disease Epidemiology Collaboration formula CKD-EPI

- when actual GFR is greater than 60 mL/min per 1.73 m2

$$eGFR = 141 \times \min(SCr/k,1)^{a} \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [1.159\ if\ Black]$$

k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males

Estimation of GFR in a pediatric patients

- **The Schwartz Equation**
- GFR can be estimated in a pediatric patient simply using plasma creatinine without all the hassle of 24-hour urine collection.
- **The equation is eGFR =**

(k * height in cm) / P_{cr} (in mg/dl)

Estimation of GFR in a pediatric patients

Example: for 6-y old child:

k = 0.55, h = 110cm, P_{cr} = 0.33mg/dl

- eGFR = (0.55 * 110) / 0.33 = 183ml/min/1.73m^2

Formulas Used To Estimate GFR

- Modification of Diet in Renal Disease (MDRD) formula
- 186 (serum creatinine in mg/dL)$^{-1.154}$ (age in years)$^{-0.203}$
-
- Cockcroft-Gault formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

- CKD-EPI formula
- Chronic Kidney Disease Epidemiology Collaboration
- Mayo Quadratic formula
- Schwartz formula

Estimating GFR in adults

- Let us take the example of an 85-year old geriatric female patient.
- Weight = 75kg, Pcr = 1.5mg/dl

- eGFR = [(140 – 85) * (75kg)] * 0.85 / (1.5 * 72) = 36ml/min/1.73 m^2

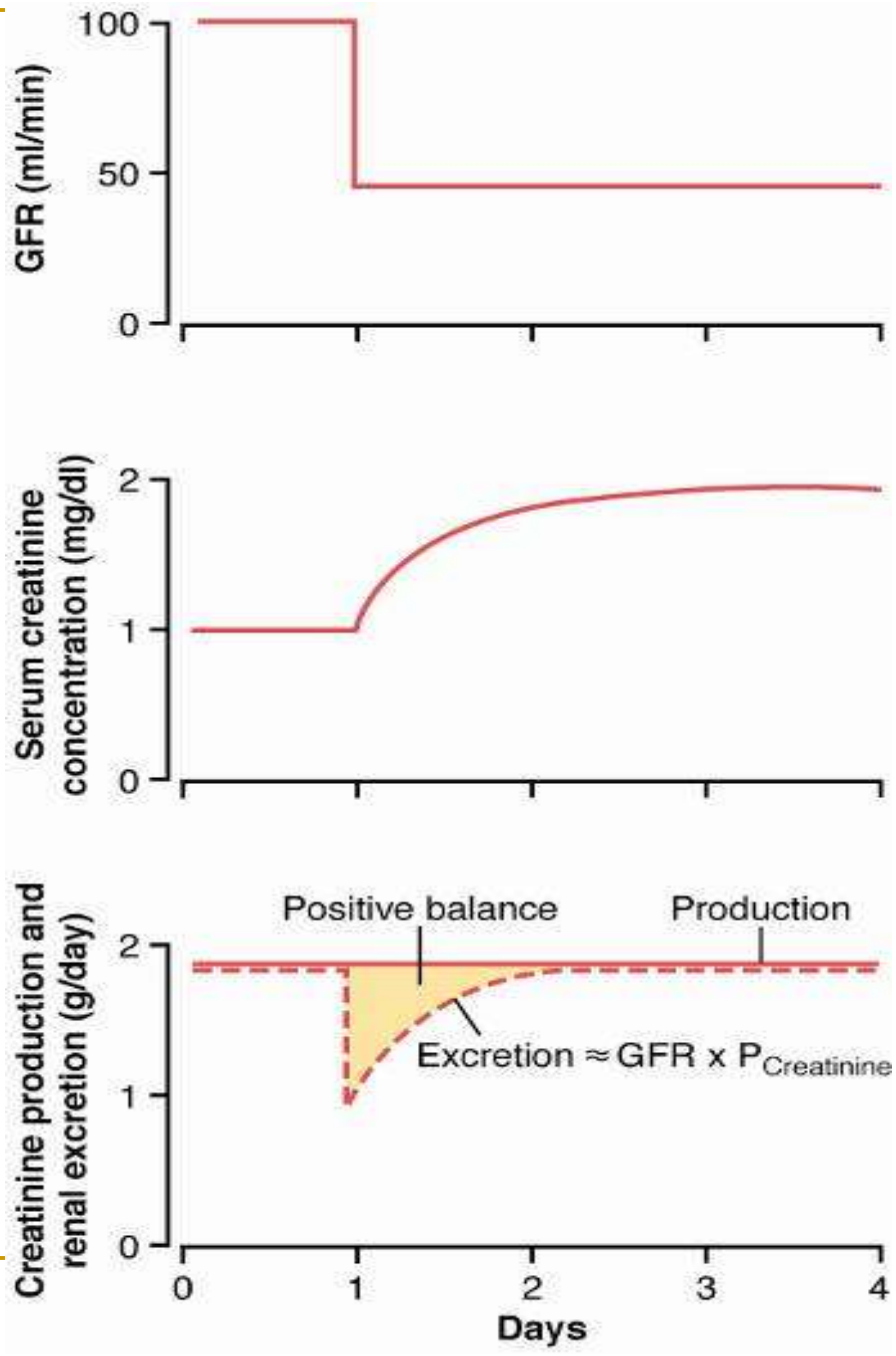
Estimating GFR in adults

- The bottom line is that equations for estimation of GFR are available and accurate. Pcr and anthropometric measures are utilized without the need for 24-hour urine collection.
- Gradual loss of renal function with age is a normal process (1% each year after the age of 40 y), as in the case of the female patient in the previous example. Although her GFR is markedly reduced, it is probable that she has normal renal function according to her age. Even if she has hypertension, it is most likely due to age-related vascular degenerative processes.
- Notice that estimations of GFR are unacceptable in cases of end-stage renal disease.

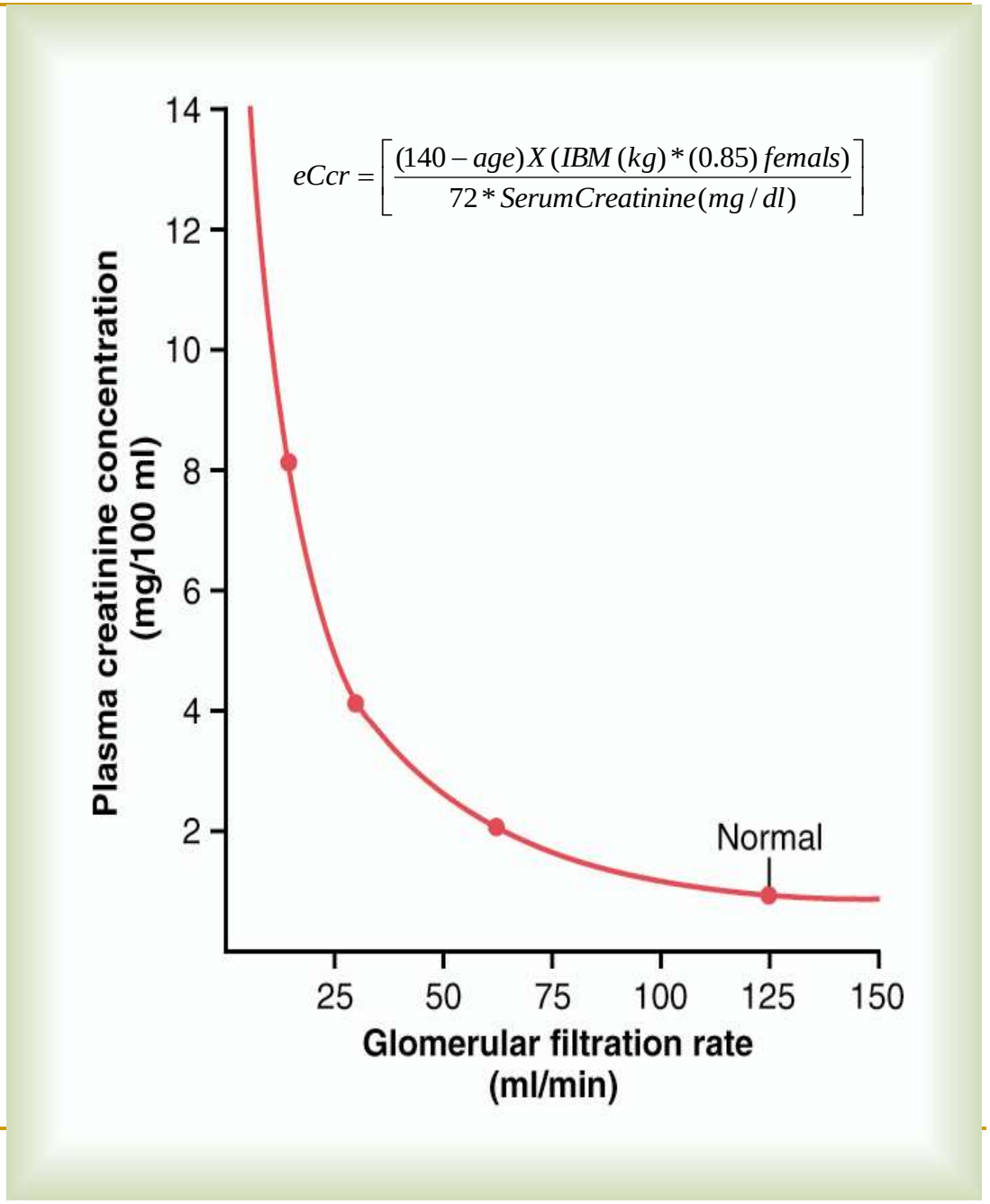
Implications of measuring GFR

- Many chronic diseases affect renal function. One major example is diabetes mellitus, which causes micro-angiopathy in the renal vasculature. This in turn alters glomerular filtration.
- You might have noticed from the example above that the GFR is way below normal, even though Pcr is slightly elevated. Kidney impairment is present, but it is not serious.

Effect of reducing GFR by 50 % on serum creatinine concentration and creatinine excretion rate

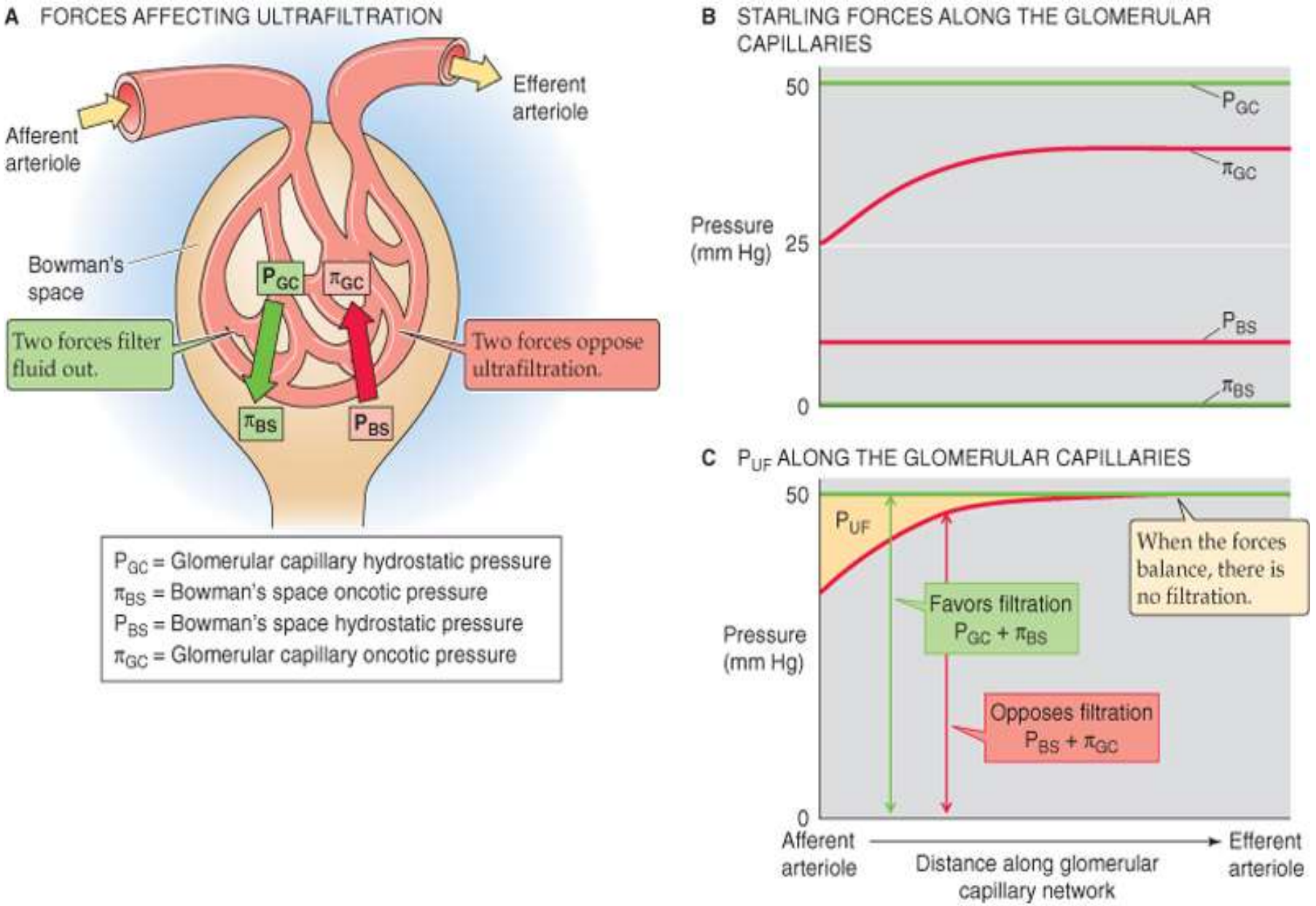


Plasma creatinine can be used to estimate changes in GFR



Filtration in systemic capillary beds VS Glomerular Filtration

- filtration across the systemic capillary bed of capillaries is only 20L/day ;17L is reabsorbed by veins and 3L by lymphatics (kidneys are not included).
- filtration through the glomerular capillaries is 180L/day;i.e., 9 times more than the systemic filtration. Why?



$GFR = Kf.[(P_{GC} - P_{BS}) - (\Pi_{GC} - \Pi_{BS})] = K_f * P_{eff}$

(use Ohm's law again)

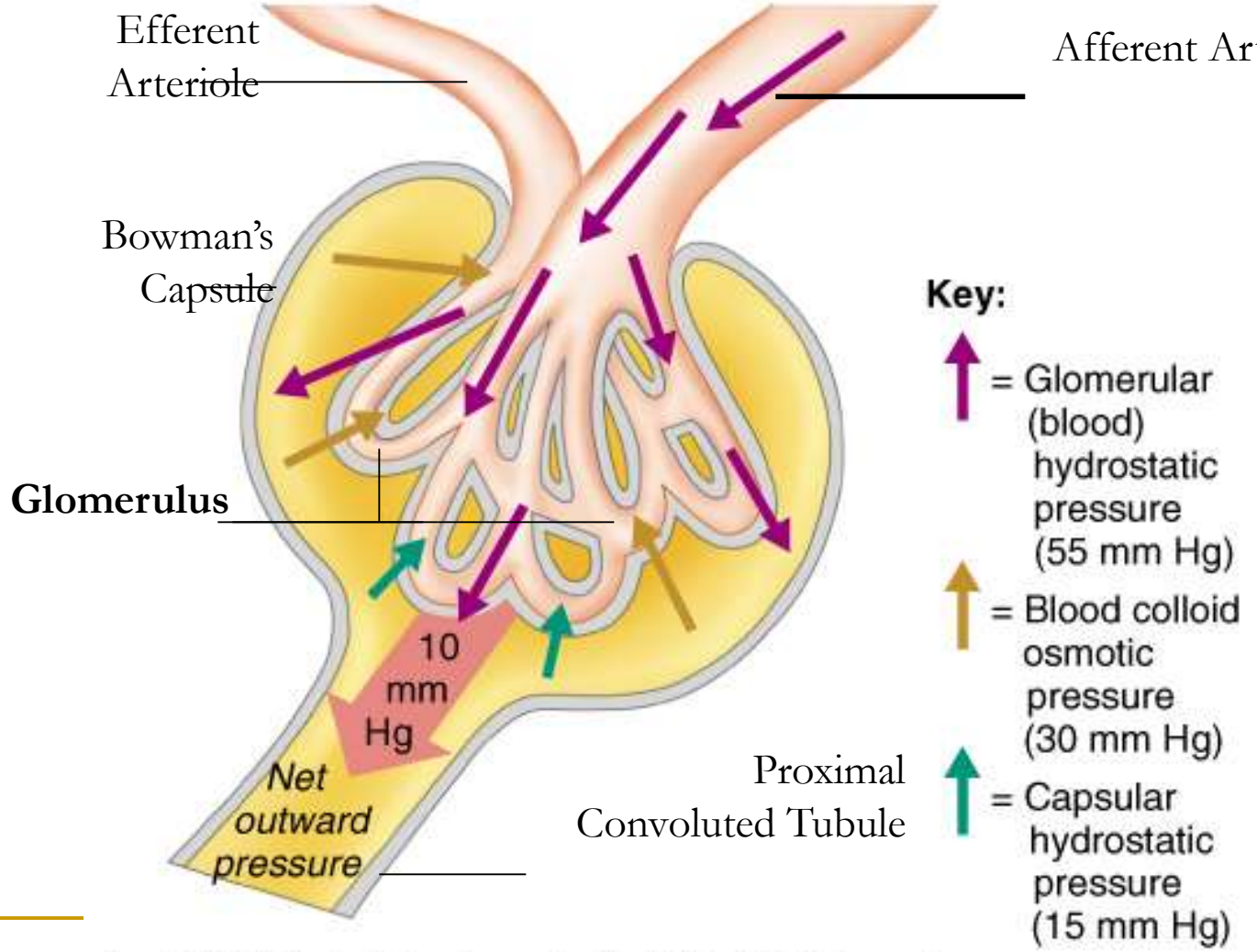
- The driving force is the summation of Starling forces which are 2 forces inside and only one force outside.
- The inside ones are:

1. Capillary hydrostatic pressure ($\mathbf{P_{GC}}$).
2. Colloid capillary pressure ($\pi_{\mathbf{GC}}$) provided by albumin and globulin mostly by albumin.

- The outside ones are:

1. $\mathbf{P_{BS}}$; it is 18 mmHg (encapsulated organs) and it will oppose filtration (in most tissue interstitial pressure is subatmospheric or –ve)

Location of the Glomerulus



Dirving Forces affecting Filtration

- Favoring Filtration:

1. Hydrostatic Pressure in the Glomerular capillaries. ($\mathbf{P_{GC}}$) =60 mmHg..the highest in our body
2. Oncotic (Colloid) Pressure of the filtrate in the Bowman's capsule. ($\Pi_{\mathbf{BS}}$)=32 mmH

- Opposing Filtration:

1. Hydrostatic Pressure in the Bowman's capsule.($\mathbf{P_{BS}}$)=18 mmHg

I.

Glomerular Hydrostatic Pressure:

- The difference between 20L/day (systemic capillaries) and the 180L/day (GFR) is either due to increased $\mathbf{P_{eff}}$ or increased Kf or both.
- The $\mathbf{P_{GC}}$ here is 60 mmHg as opposed to 20-40 mmHg in systemic capill, or 7-10 mmHg in pulmonary capillaries…..WHY?
- If we look at systemic capillaries, they have an arteriolar end and a venular end but in the glomeruli they have both arteriolar ends (afferent and efferent arterioles). This makes the pressure in the glomerular capillaries the highest (60 mmHg) in our body. The efferent is narrower.

Arteriolar diameter effect on GFR:

- Afferent **dilatation** means an increase in the blood coming to the capillaries so increased P_{GC} and GFR.
- **Constriction** of efferent arteriole increases P_{GC} to a limit. If it goes over this limit filtration will decrease as no more blood entering the capillaries.
- To regulate P_{GC} you either control the afferent arteriolar dilatation or the efferent arteriolar constriction or both.

II. Glomerular Capillaries Oncotic(colloid) Pressure:

- In the **systemic** capillaries the Π stays 28mm Hg at both the arterial and venous ends. WHY?

Because what is filtered is only 0.5% from the whole incoming fluid, Π so it does not affect the concentration of proteins much.

- But filtration in the **kidneys** is 20% so it must have an effect so Π_{GC} that becomes 36mm Hg at the efferent end (avg. 32 mmHg).

III. Interstitial forces (Bowman's Space) :

- Bowman's Space contains protein free glomerular filtrate; i.e, too small Π_{BS}.

So in the kidneys Starling forces have been reduced to 3 forces instead of 4 forces

- Hydrostatic Pressure (P) of Bowman's space is 18 mmHg due to the fluids filtered.
- **Net Driving forces favoring filtration=**

60 – (32 + 18) = 10 mmHg

- **Knowing that P = 10mmHg and GFR is 125 then K_f will equal =12.5 ml/min.mmHg**
- **(125=10*KF)**

Renal K_f

Basement membrane is negatively charged

- In nephrotic syndrome, loss of negative charge causes albumin loss and edema (Alb MW is slightly less than 70K but still not filtered bcs it is negatively charged. When basement membrane losses its negative charge …now albumin can filter leading to hypoalbuminemia.).
- (Remember the four cause of hypoalbuminemia : malnutrition, malabsorption, malproduction, and increased loss from the kidney).
- Hypoalbuminemia →↑GFR.

Renal Autoregulation

- **Autoregulation of** GFR…see the figure after 3 slides
- GFR is fluctuates slightly in relation to changes in arterial blood pressure but this translates in a large increase in urine output… why is that?
- GFR = 125ml/min and UOP is only = 1ml/min = 1.5L/day which means 124ml/min is reabsorbed (99.4% of the filtered water is reabsorbed and only 0.6% is excreted) so a little change in GFR changed the urine output a lot.
- Therefore, GFR must be regulated and this is achieved mainly by the renal vascular system (glomerular capillary hydrostatic pressure) and this is controlled by afferent and efferent arterioles by the following mechanism:

Tubuloglomerular Feedback

- In the distal tubule the afferent arteriole touches a few cells in its wall…these DT cells are sensors (macula densa). They sense the content of Na^+, K^+, Ca^{++} . When the amount of these electrolytes reach macula densa is small → 2 messages are sent.

1. **The first message**: dilatation of the afferent arteriole so the blood flow increases to the capillaries. (Myogenic Response)
2. **The second message**: is to the granular cell in the afferent arteriole to secret rennin (hormonal response).

- Rennin leaves the kidney and goes to the circulation where it cleaves 4 amino acids for a 14-aa small peptide produced by the liver and called angiotensinogen forming the decapeptide angiotensin-I . In the lungs the ACEs (angiotensin converting enzymes) convert AI to AII (octapeptide).
- In bleeding we have to protect the kidneys by keeping normal GFR and at the same time conserve water. Angiotensin-II can do this…through

Tubuloglomerular Feedback

- **First**: constriction of efferent arteriole leading to increased GFR and at the same time the pressure in the peritubular capillaries decreases giving a better chance for reabsorbing to get the minimal urine output which is 0.5L/day.
- **Second**: angiotensin acts directly on the adrenal cortex to secret aldosterone that enhances the reabsorption of Na+ from the distal tubule and sodium bring with it water.
- **Third**: angiotensin itself act directly to enhance sodium reabsorption in the proximal tubule.

Bowman's Capsule hydrostatic Pressure (P_B)

- Normally changes as a function of GFR, not a physiological regulator of GFR
- Tubular Obstruction
  - kidney stones
  - tubular necrosis
- Urinary tract obstruction
  - Prostate hypertrophy/cancer

Factors Influencing Glomerular Capillary Oncotic Pressure (π_G)

- Arterial Plasma Oncotic Pressure (π_A)

$\uparrow \pi_A \longrightarrow \uparrow \pi_G$

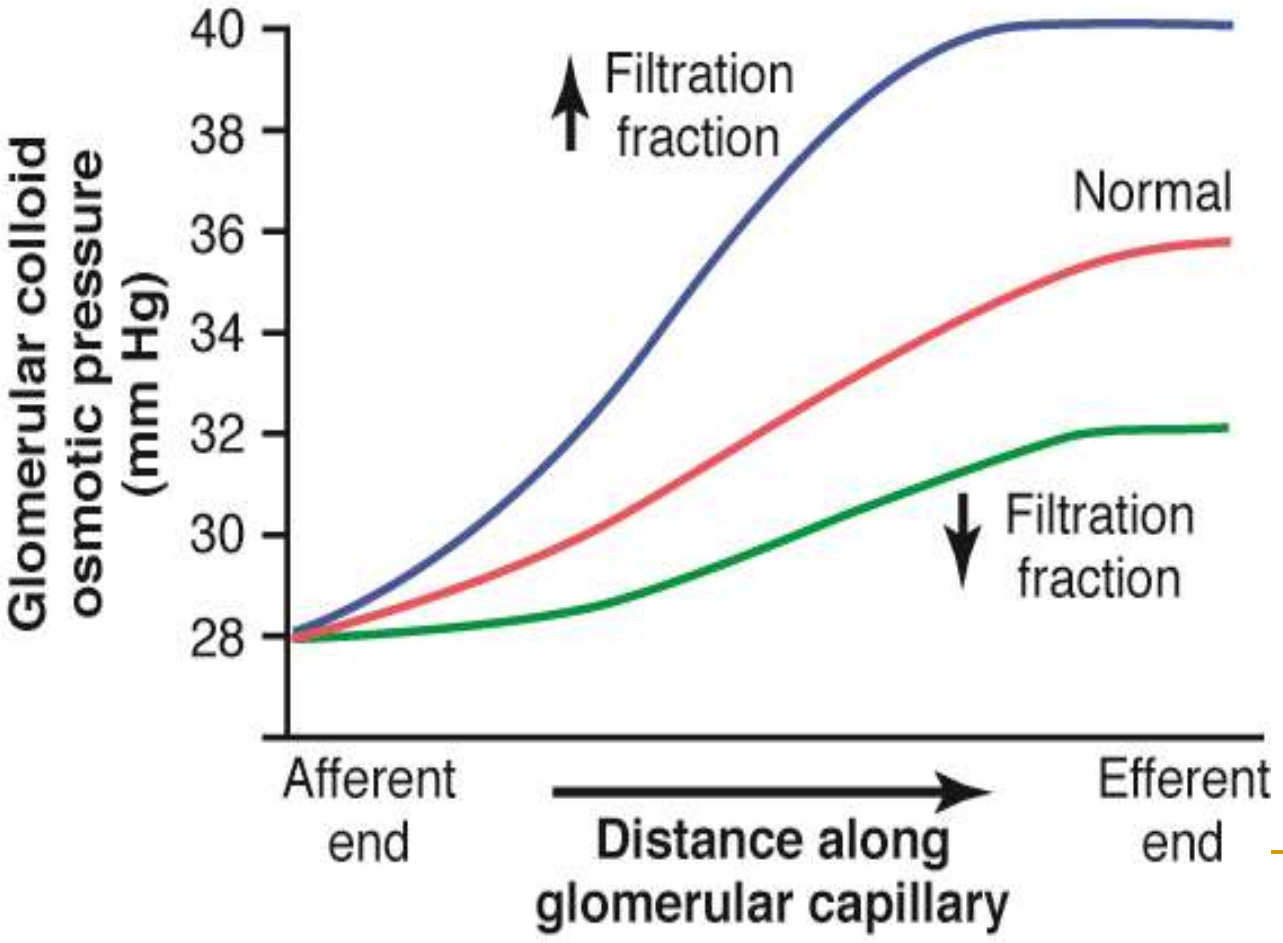
- Filtration Fraction (FF)

$\uparrow$ FF $\longrightarrow \uparrow \pi_G$

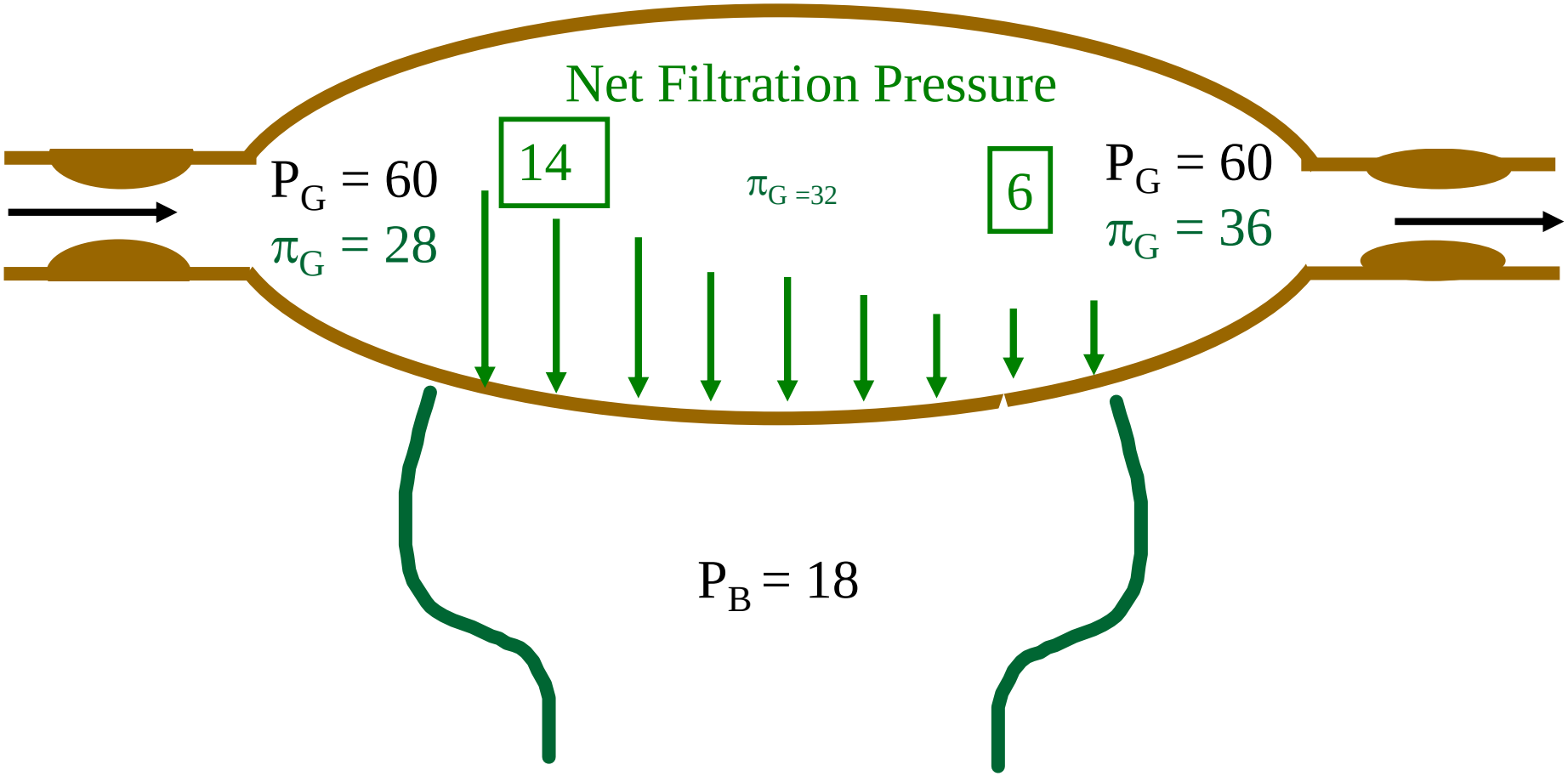
FF = GFR / Renal plasma flow

= 125 / 650 ~ 0.2 (or 20%)

Increase in colloid osmotic pressure in plasma flowing through glomerular capillary



Net Filtration Pressure Decreases Along the Glomerulus Because of Increasing Glomerular Colloid Osmotic Pressure



Measuring GFR

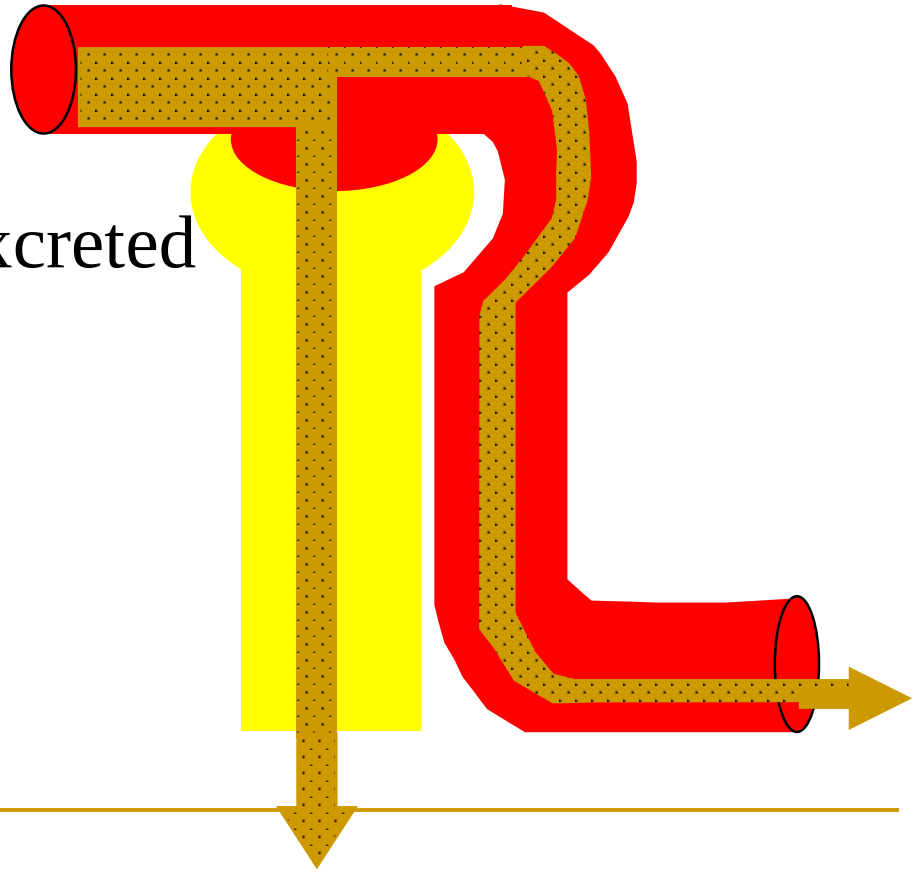
- The concept of Clearance…make sure you understand this concept fully…it is the most important concept in renal physiology…it tells you how the nephron or any segment of the nephron handles any substance…for instance we use the clearance to measure GFR, RPF etc Given the concentration of a substance in the plasma and the amount of the substance excreted in the urine per minute, you will compute the plasma clearance rate.

Measurement of GFR = C_{inulin}

Inulin is a starch-like polymer of fructose (MW 5000).Inulin is a glomerular marker. **$C_{creatinine}$**…instead of inulin we use creatinine… we either use tGFR or eGFR (“t” stands for true and “e” stands for estimated)

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

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

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

Creatinine MW 114

The typical reference ranges are: Men 0.7 to 1.2 mg/dL (60-110 μmol/l), for women: 0.5 to 1.0 mg/dL (about 45-90 μmol/l) . While a baseline serum creatinine of 2.0 mg/dL (150 μmol/l) may indicate normal kidney function in a male body builder, a serum creatinine of 0.7 mg/dL (60 μmol/l) can indicate significant renal disease in a frail old woman.

In the United States, creatinine is typically reported in mg/dL, while in Canada and Europe μmol/litre may be used.

1 mg/dL of creatinine is 88.4 μmol/L.

Plasma Clearance

Let us practice calculating plasma clearance using the clearance equation. In all your calculations, assume that the urine production rate (V) is 2 ml/min. Let's start with the substance inulin (not insulin not ihibin!). If after a dose of inulin, your urine has 30 mg/ml and your plasma has 0.5 mg/ml of this substance, what is the inulin clearance rate? If you got 120ml/min, you are correct!

120 ml/min = 2 ml/min x 30 mg/ml/ 0.5 mg/ml

Clearances of Different Substances

Substance	Clearance (ml/min)
glucose	0
albumin	0
sodium	0.9
urea	70
inulin	125
creatinine	140
PAH	600

Plasma Clearance

Test your ability to conduct further calculations by calculating the clearance rate for the following substances:

Substance	Urine concentration	Plasma concentration
Urea	7.0 mg/ml	0.2 mg/ml
Glucose	0.0 mg/ml	1.0 mg/ml
Penicillin	298 mg/ml	0.7 mg/ml

Urine production rate is (2ml/min). The clearance rate for each of the above substances will be: **Urea** = 70 ml/min; **Glucose** = 0 ml/min; **Penicillin** = 851 ml/min…doesn't make sense!!!. Were you able to get the right answers? If not, go back and restudy the clearance process.

- Since Inulin is an exogenous substance it is only used for research purposes and not as a clinical test.

•We need an endogenous substance: **<u>Creatinine</u>**. Creatinine: Comes from high energy bound, muscle phosphocreatinine (PC).

- ***Is muscle protein***
- ***Small molecule (MW is 114))***
- ***Its concentration does not fluctuate from day to day in plasma***

- ***Freely filtered, not reabsorbed but SLIGHTLY SECRETED***

To convert μmol /l of creatinine to mg/dl, divide by 88.4.

To convert mg/dl of creatinine to μmol/l, multiply by 88.4

Creatinine in the urine comes from 90% filtered and 10% through secretion. This has the potential to overestimates GFR by 10%. But in actuality it does not…why? In fact, it does overestimate GFR in end-stage renal failure…again WHY? Look for the answer in both cases

- Creatinine: Comes from high energy bound, muscle phosphocreatinine (PC)
- Plasma creatinine by itself (without creatinine clearance) is a good indicator of renal function because it does not relate to food intake or level of exercise.

Through this equation:

$$\text{Creatinine Clearance} = C_{cr} = GFR = \frac{U_{Cr}}{P_{Cr}} * V$$

Last point : 10% of Cr in urine is secreted which will overestimates the GFR.
But it was found that 10% of Cr in plasma is bounded to protein… it is the total Cr we measure and not only the free portion. (so, both factors cancel each others).

Ccr is good estimate for GFR.

Plasma Clearance

The formula used to calculate plasma clearance is:

$$C = V \times U/P$$

C = plasma clearance rate in ml/min

V = urine production rate in ml/min

U = the concentration of a substance in the urine in mg/ml

P = the concentration of a substance in the plasma in mg/ml

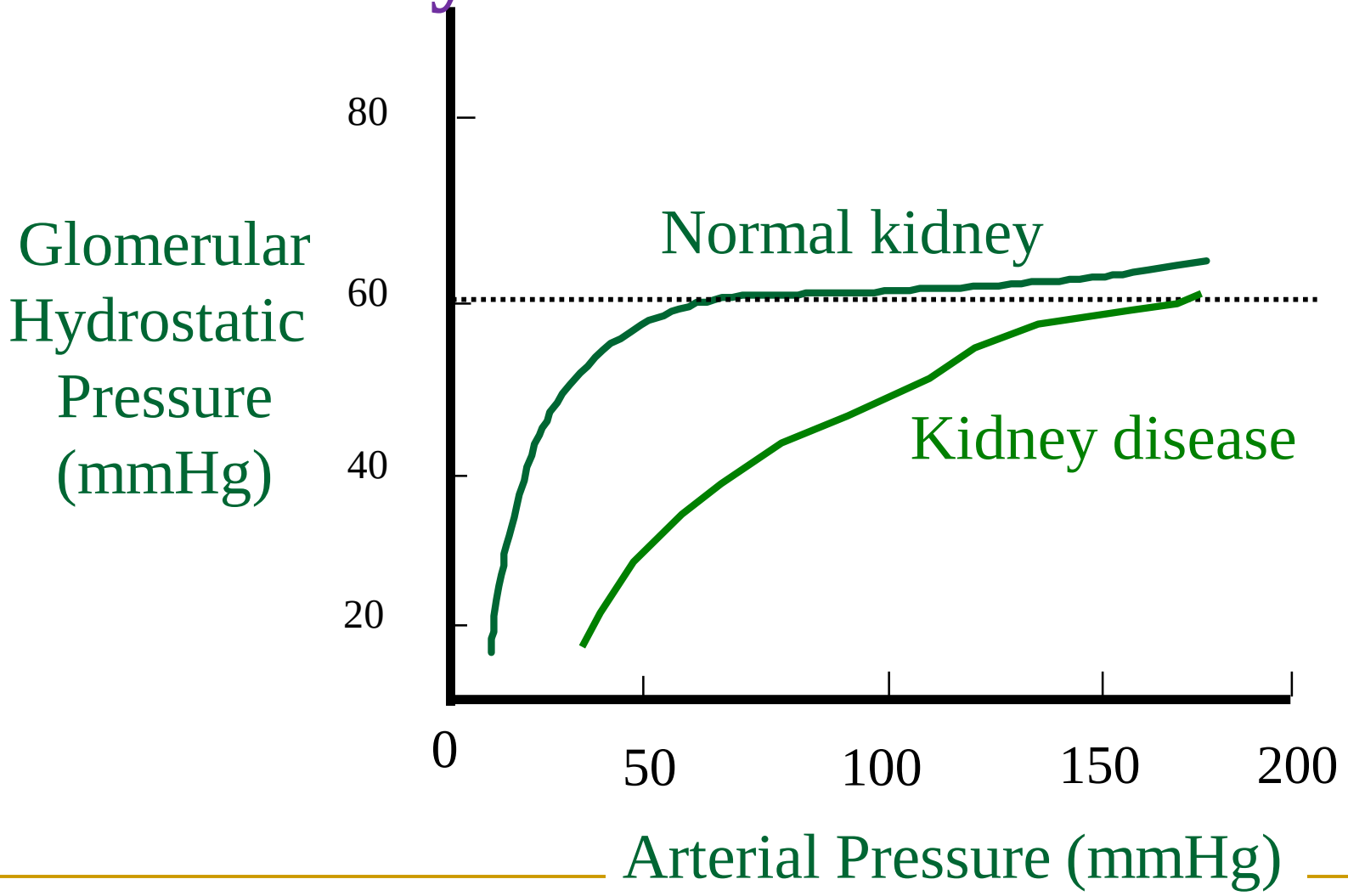
As you track the units in the equation, you will notice that mg/ml cancel out, leaving ml/min.

Glomerular Hydrostatic Pressure (P_G)

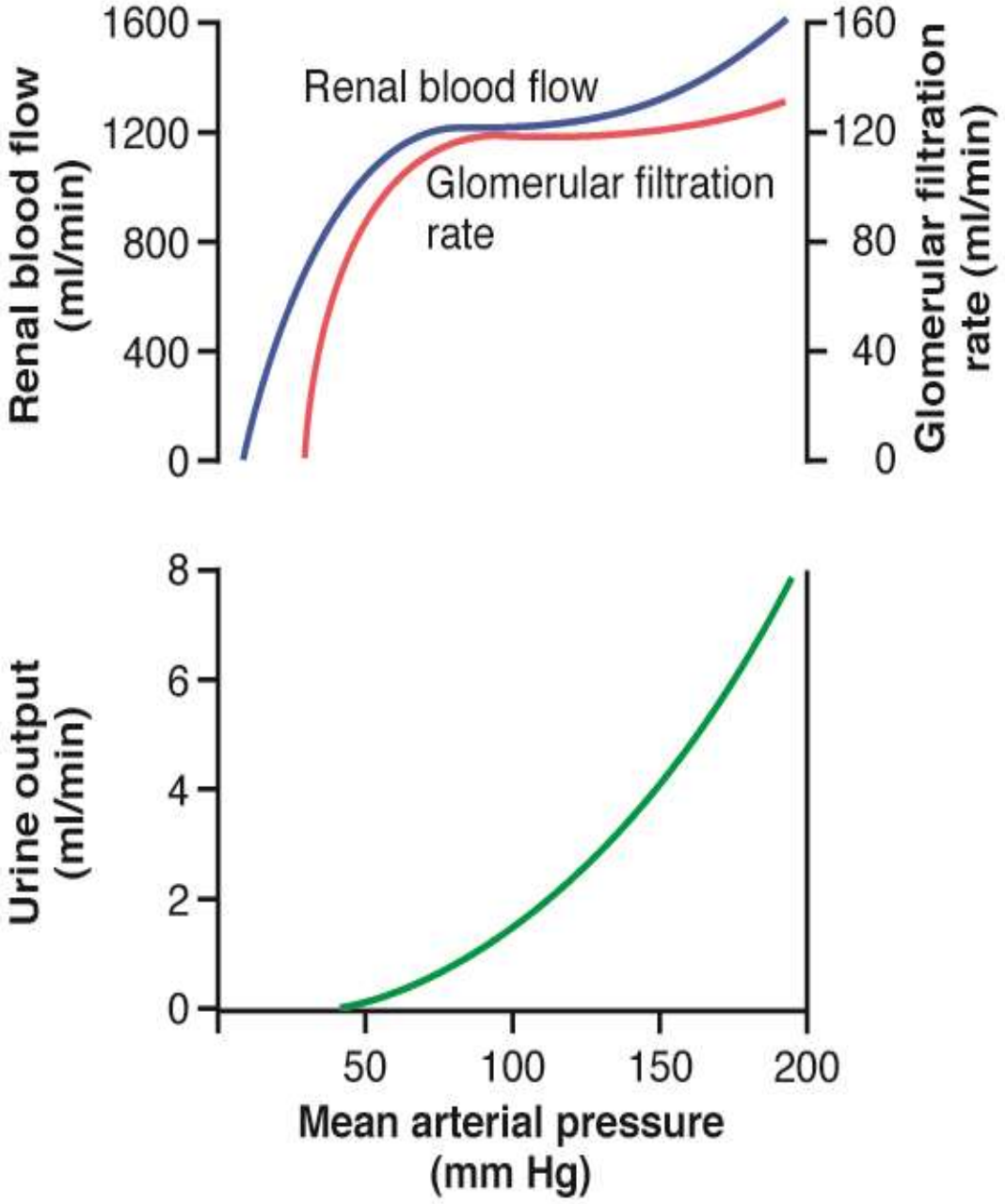
- Is the determinant of GFR snd is subject to physiological control

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

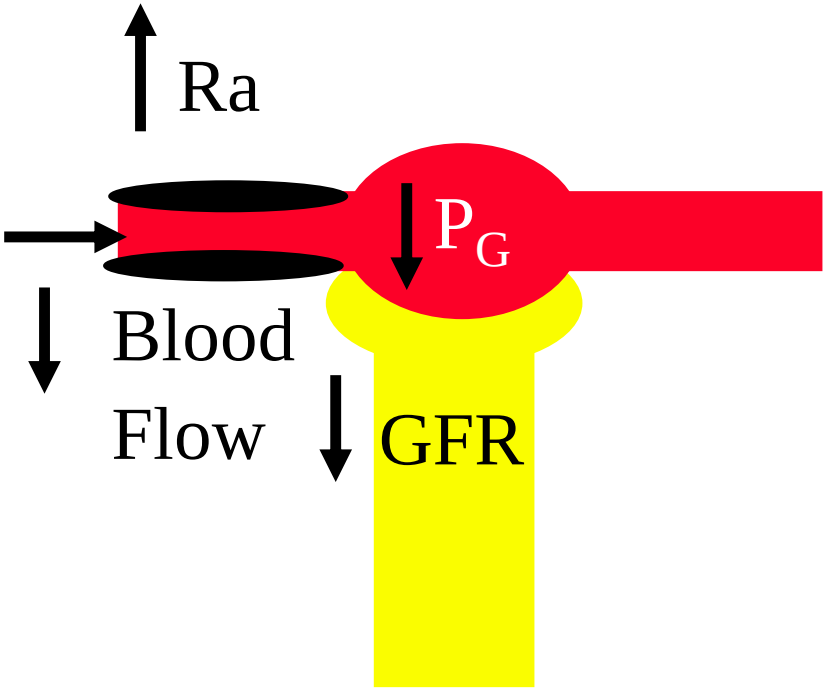
Autoregulation of Glomerular Hydrostatic Pressure

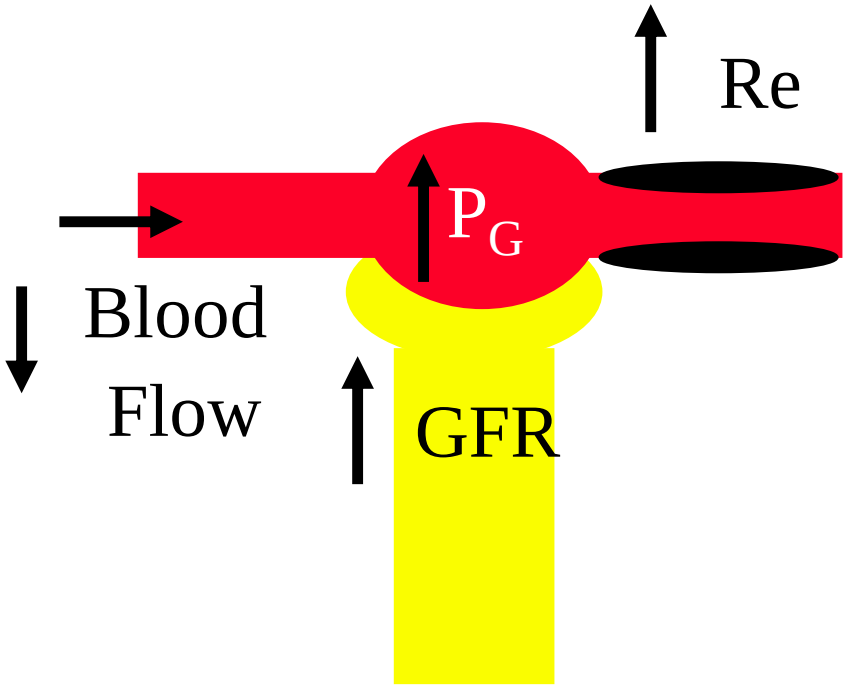


Autoregulation of renal blood flow and GFR but not urine flow



Effect of afferent and efferent arteriolar constriction on glomerular pressure





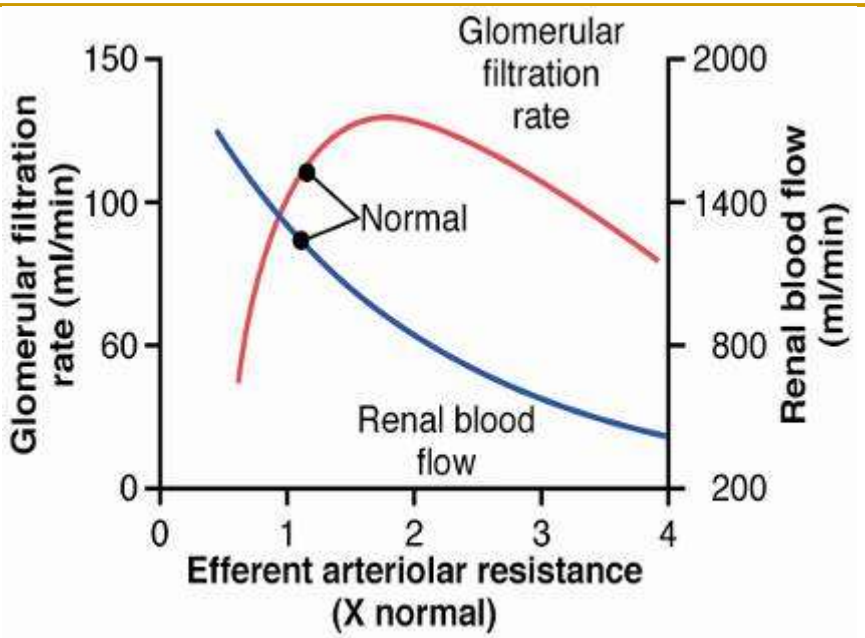
Ra → GFR + Renal

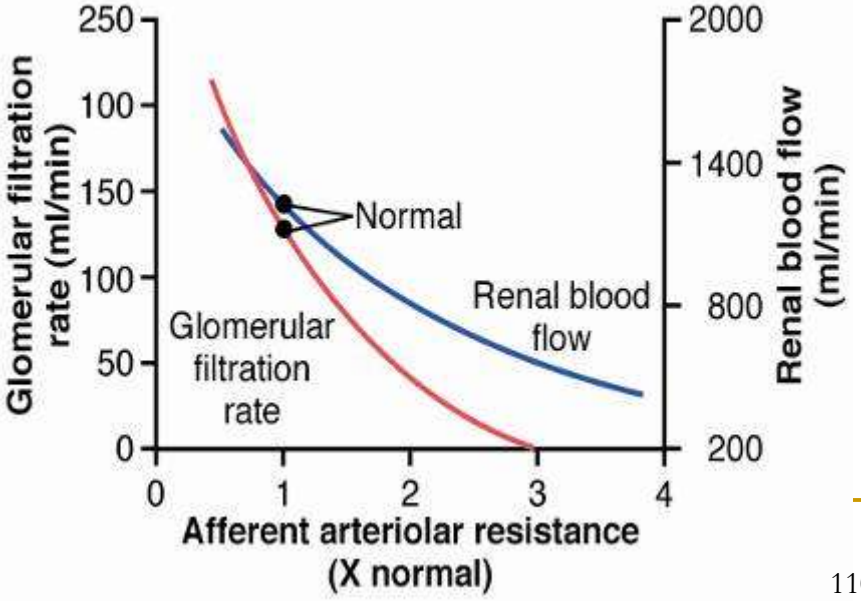
Blood flow

Re → GFR + Renal

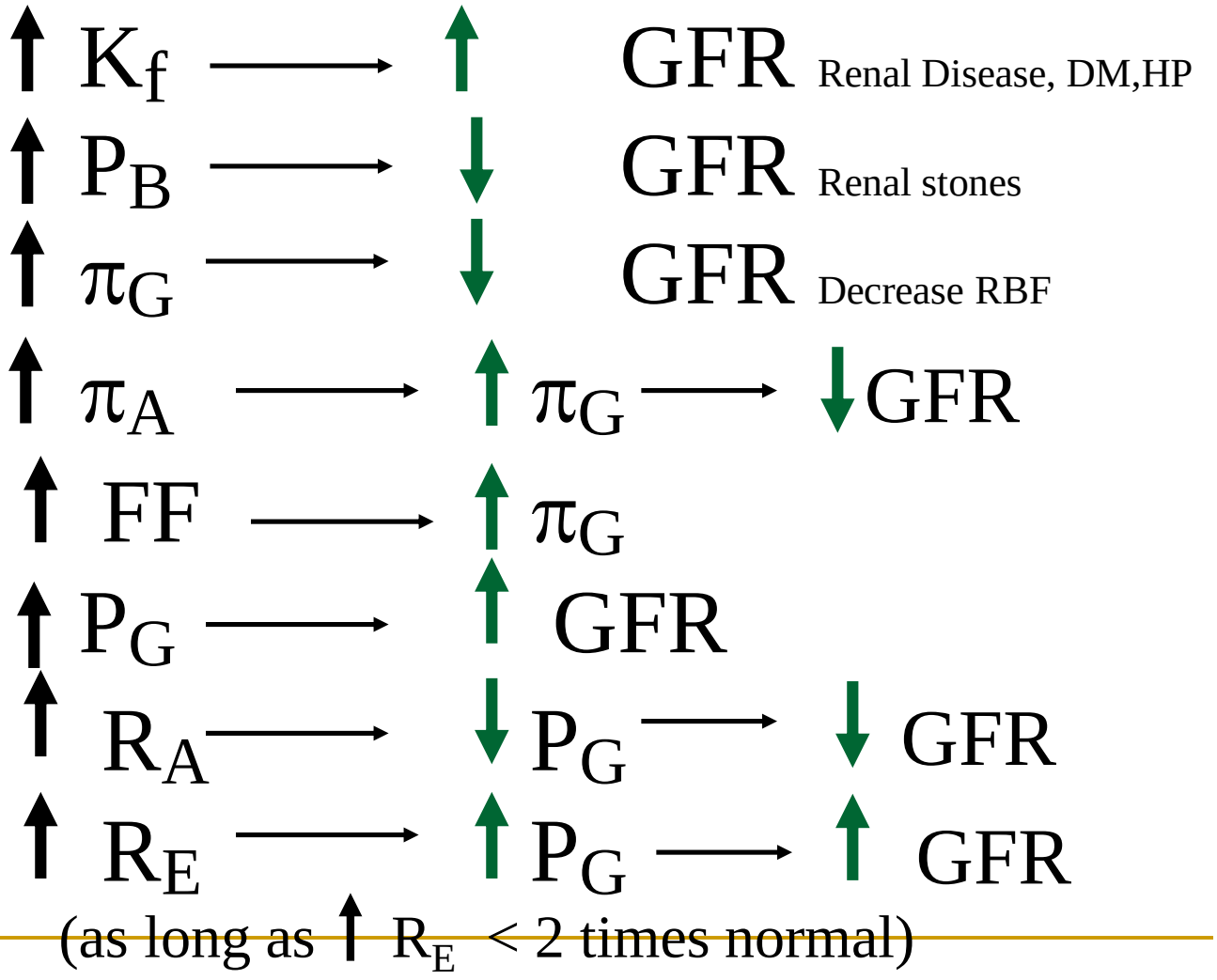
Blood flow

Effect of changes in afferent arteriolar or efferent arteriolar resistance. Biphasic Effect





Summary of Determinants of GFR



Determinants of Renal Blood Flow (RBF)

$$RBF = \Delta P / R$$ renal vascular resistance

ΔP = difference between renal artery pressure and renal vein pressure

= 100-4 mmHg

R = total renal vascular resistance

= Ra + Re + Rv

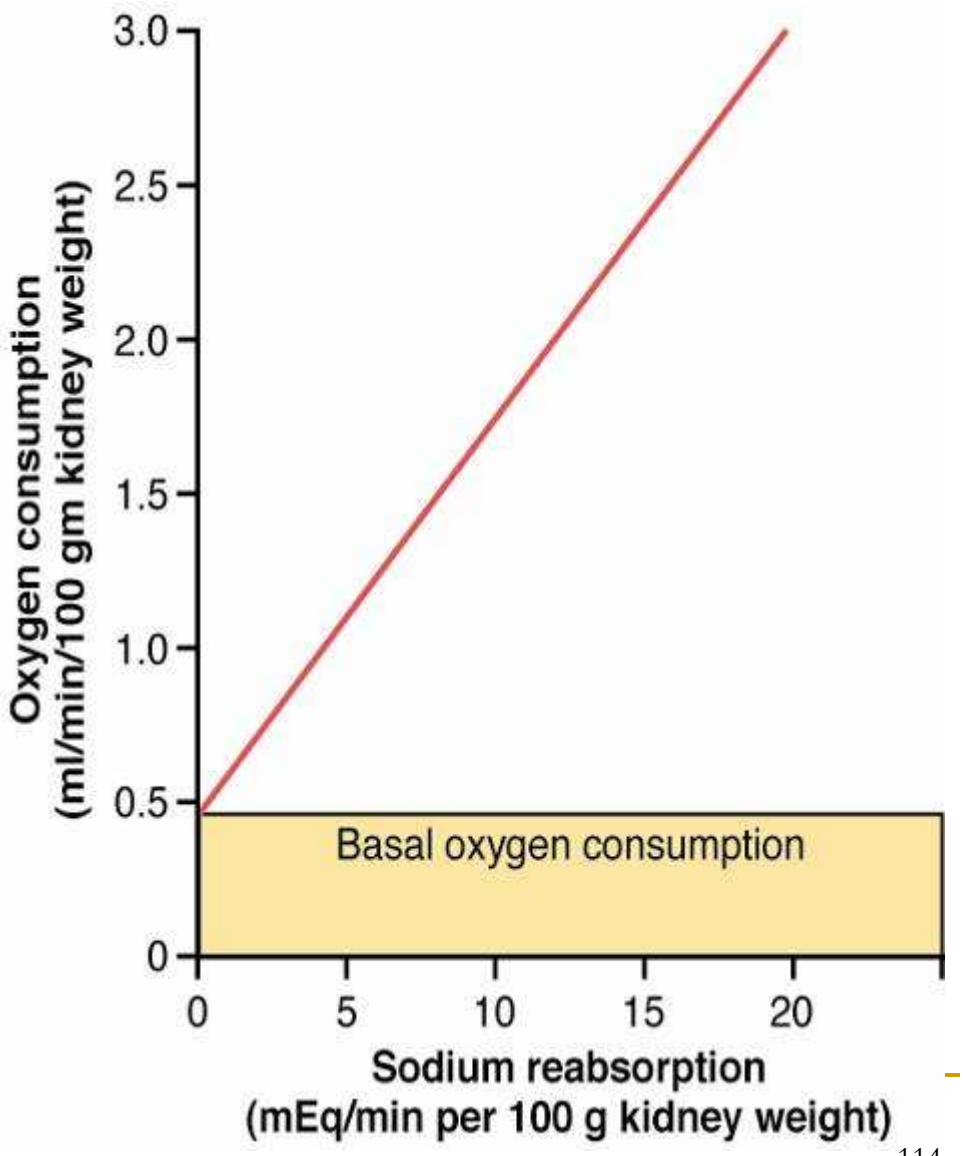
= sum of all resistances in kidney vasculature

Table 26-3. Approximate Pressure and Vascular Resistances in the Circulation of Normal Kidney

Afferent + efferent contribute to about 70% of the intrarenal vascular resistance (mainly efferent).

	Pressure mmHg		% Total Vascular R
	Beginning	End	
Renal Artery	100	100	≈ 0
Interlobar, arcuate and interlolbular arteries	100	85	15
Afferent	85	60	25
Glomerular capillaries	60	59	1 only 1mmHg which means little resistance
Efferent	59	18	43 resistance mainly resides her
Peritubular Capillaries	18	8	10
Interlobar, arcuate and interlolbular veins	8	4	4
Renal vein	4	≈4	0

Renal oxygen consumption and sodium reabsorption



Control of GFR and renal blood flow

- Neurohumoral
- Local (Intrinsic)

Renal Blood Flow

- We expect

  Flow to be a function of Pressure Gradient

- We find

  Flow to be constant

- Therefore:

  Vascular Resistance changes in response to a change in Blood Pressure

Control of GFR and renal blood flow

1. Sympathetic Nervous System /catecholamines

$\uparrow\uparrow R_A + \uparrow R_E \longrightarrow \downarrow$ GFR + $\downarrow\downarrow$ RBF

e.g. severe hemorrhage.

Under normal conditions Sympathetic tone have little influence on RBF.

Sympathetic system may not influence RBF under normal circumstances, but in severe sympathetic stimulation it may decrease RBF significantly

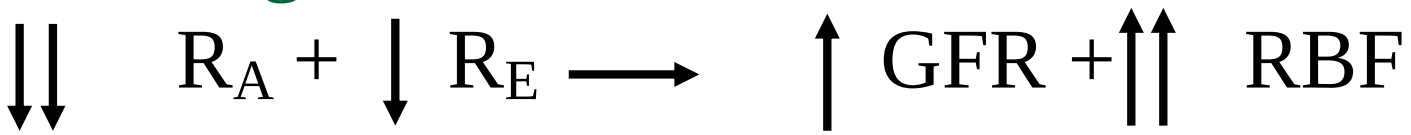
2. Angiotensin II

$\uparrow R_E \longrightarrow \longleftrightarrow$ GFR + $\downarrow$ RBF

(prevents a decrease in GFR)

e.g. low sodium diet, volume depletion

3. Prostaglandins



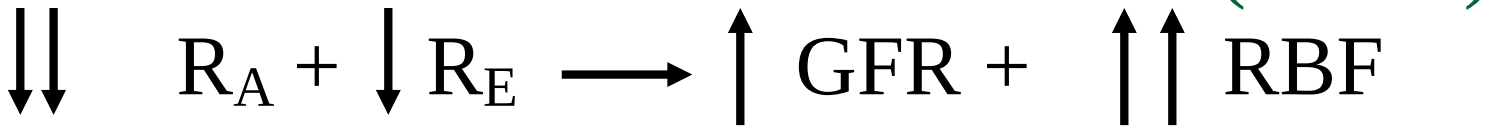
Blockade of prostaglandin synthesis → ↓ GFR

This is usually important only when there are other disturbances that are already tending to lower GFR. If Aspirin is administered which suppresses PGs then a severe decrease in GFR might occur.

e.g. nonsteroidal antiinflammatory drugs NDAID in a volume depleted patient, or a patient with heart failure, cirrhosis, etc

Control of GFR and renal blood flow

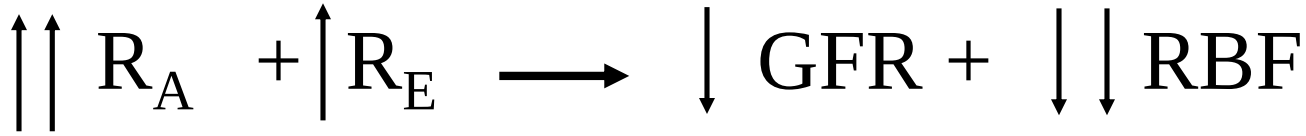
4. Endothelial-Derived Nitric Oxide (EDRF)



- Protects against excessive vasoconstriction
- Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR in response to stimuli such as volume depletion

Control of GFR and renal blood flow

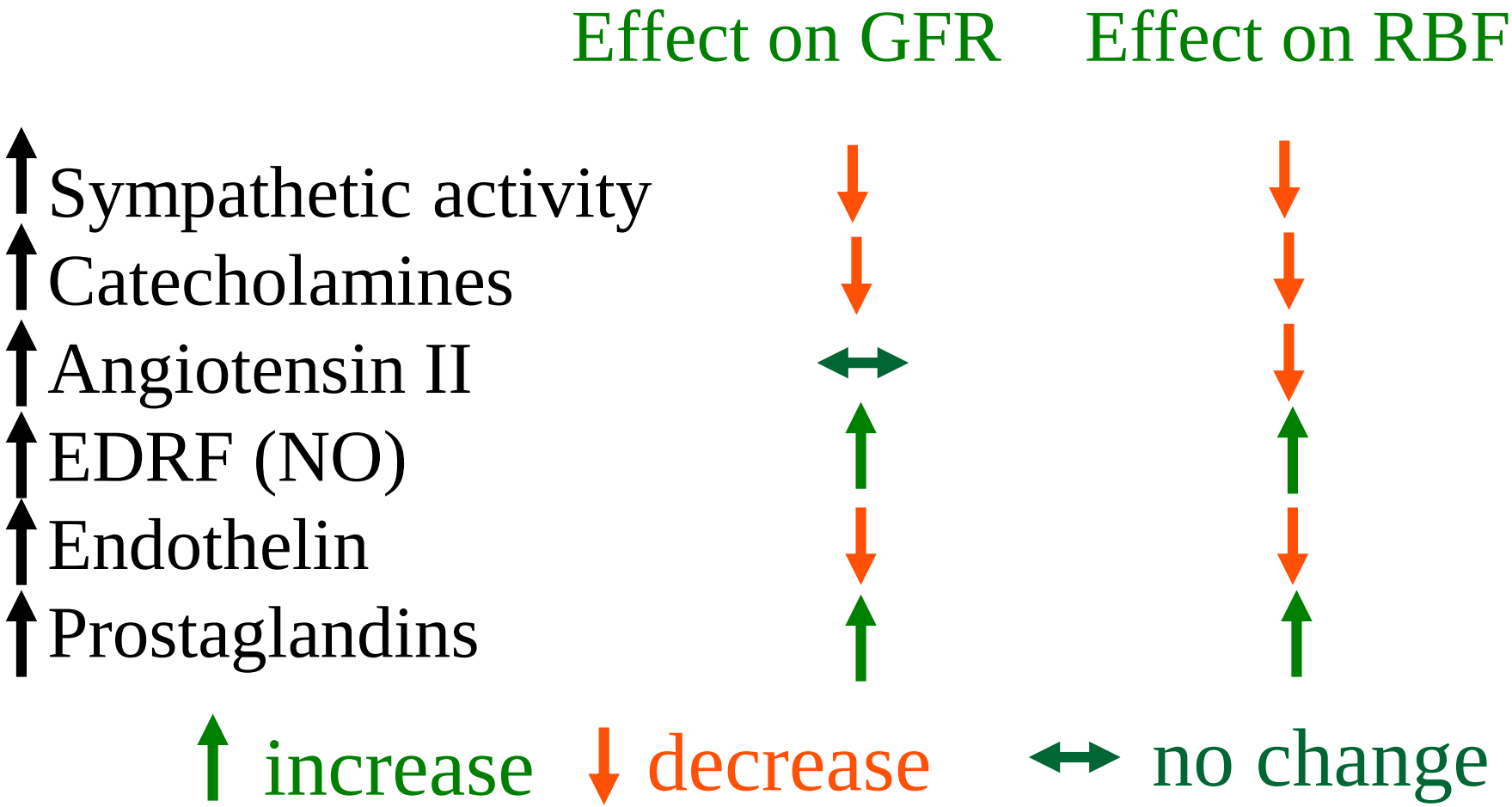
5. Endothelin



- Hepatorenal syndrome – decreased renal function in cirrhosis or liver disease?
- Acute renal failure (e.g. contrast media nephropathy)?
- Hypertensive patients with chronic renal failure?

Endothelin antagonists may be useful in these conditions

Summary of neurohumoral control of GFR and renal blood flow

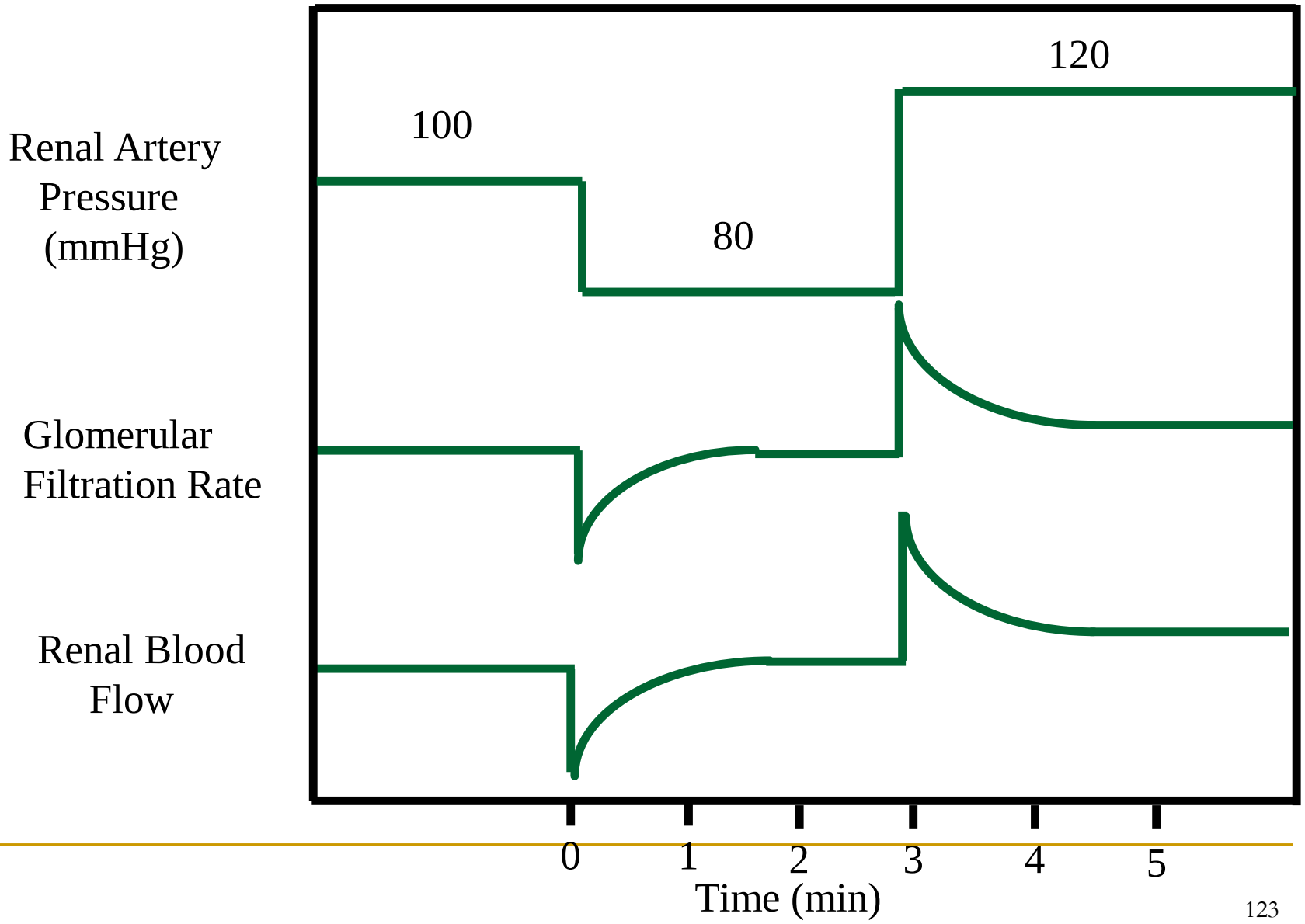


Local Control of GFR and renal blood flow

7. Autoregulation of GFR and Renal Blood Flow

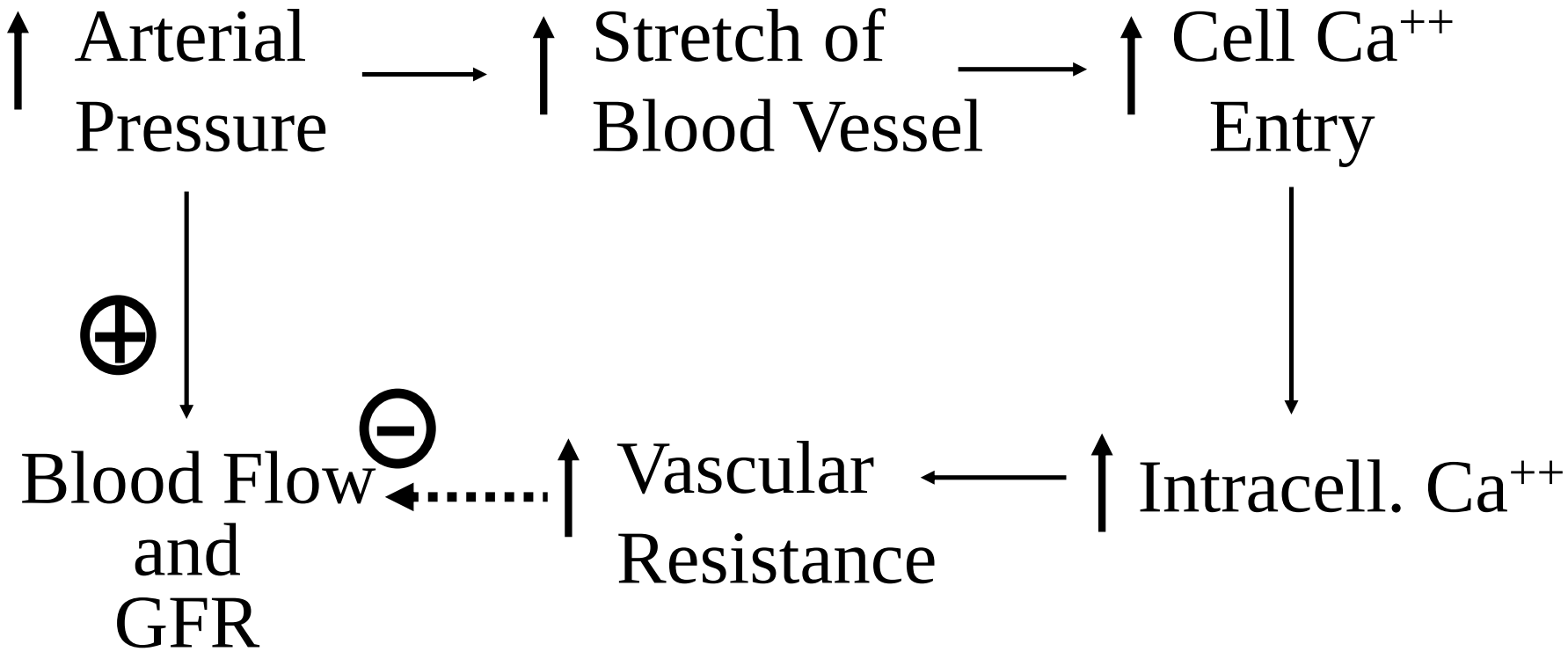
- Myogenic Mechanism
- Macula Densa Feedback
  (tubuloglomerular feedback)
- Angiotensin II (contributes to GFR but
  not RBF autoregulation)

Renal Autoregulation

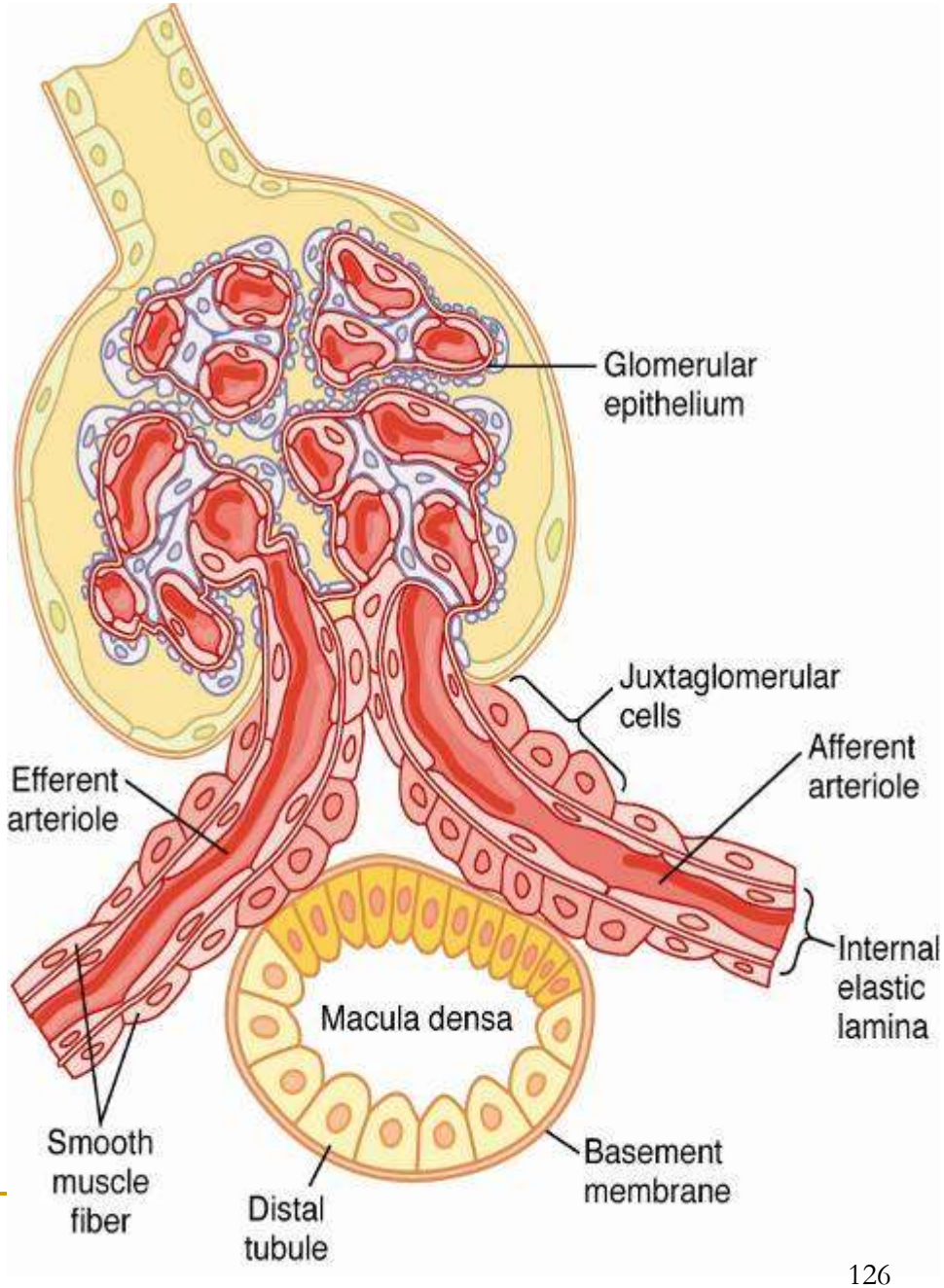


Importance of Autoregulation

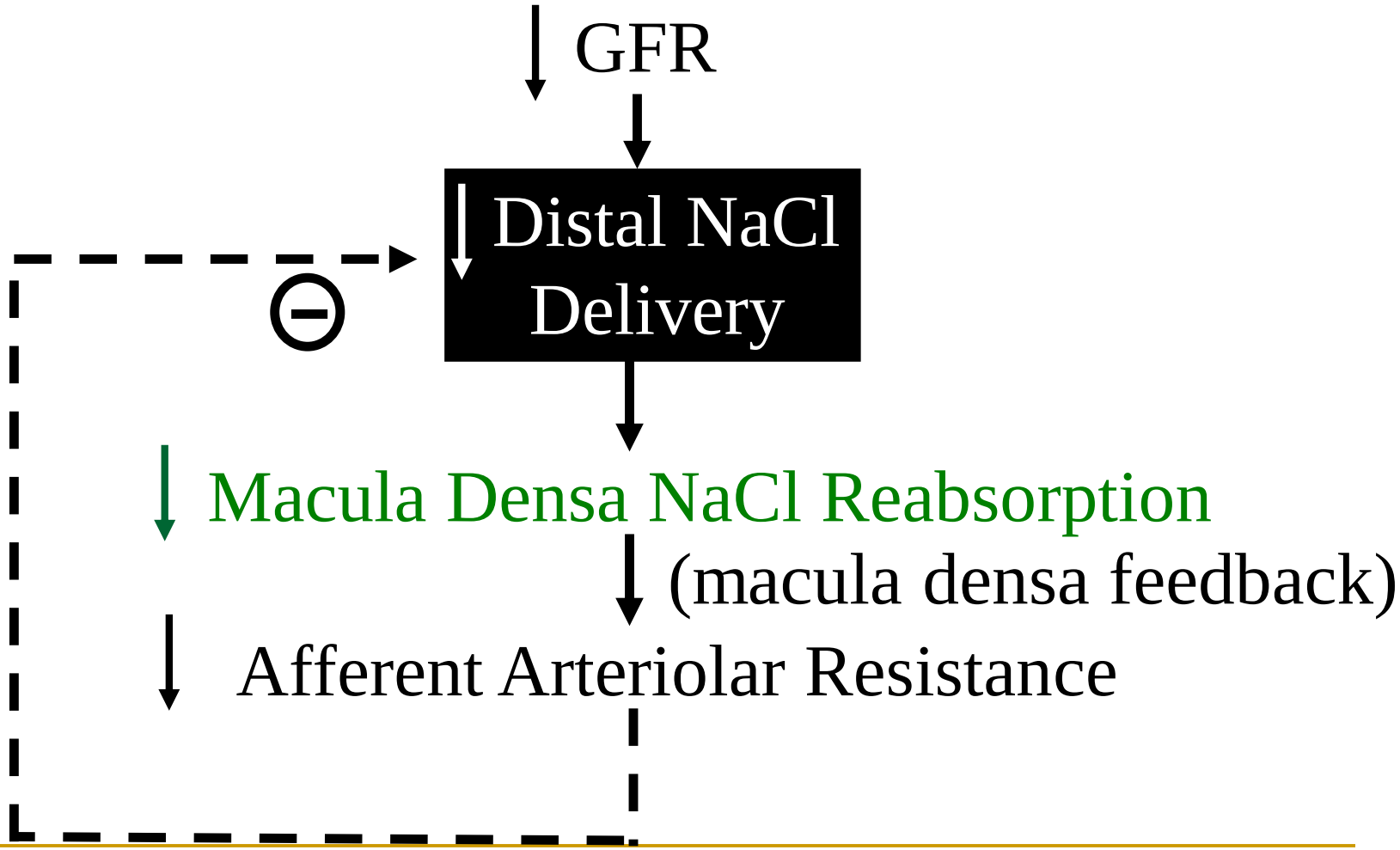
Arterial Pressure	GFR	Reabsorption	Urine Volume
1- Poor Autoregulation + no change in tubular reabsorption			
100	125	124	1.0
120	150	124	26.0 = 37.4 L/day!
2- Good Autoregulation + no change in tubular reabsorption			
120	130	124	6.0
3 Good Autoregulation+adaptive increase in tubular reabsorption			
120	130	128.8	1.2


↑ Arterial Pressure
↑ Stretch of Blood Vessel
↑ Cell Ca++ Entry
⊕
⊖
Blood Flow and GFR
↑ Vascular Resistance
↑ Intracell. Ca++

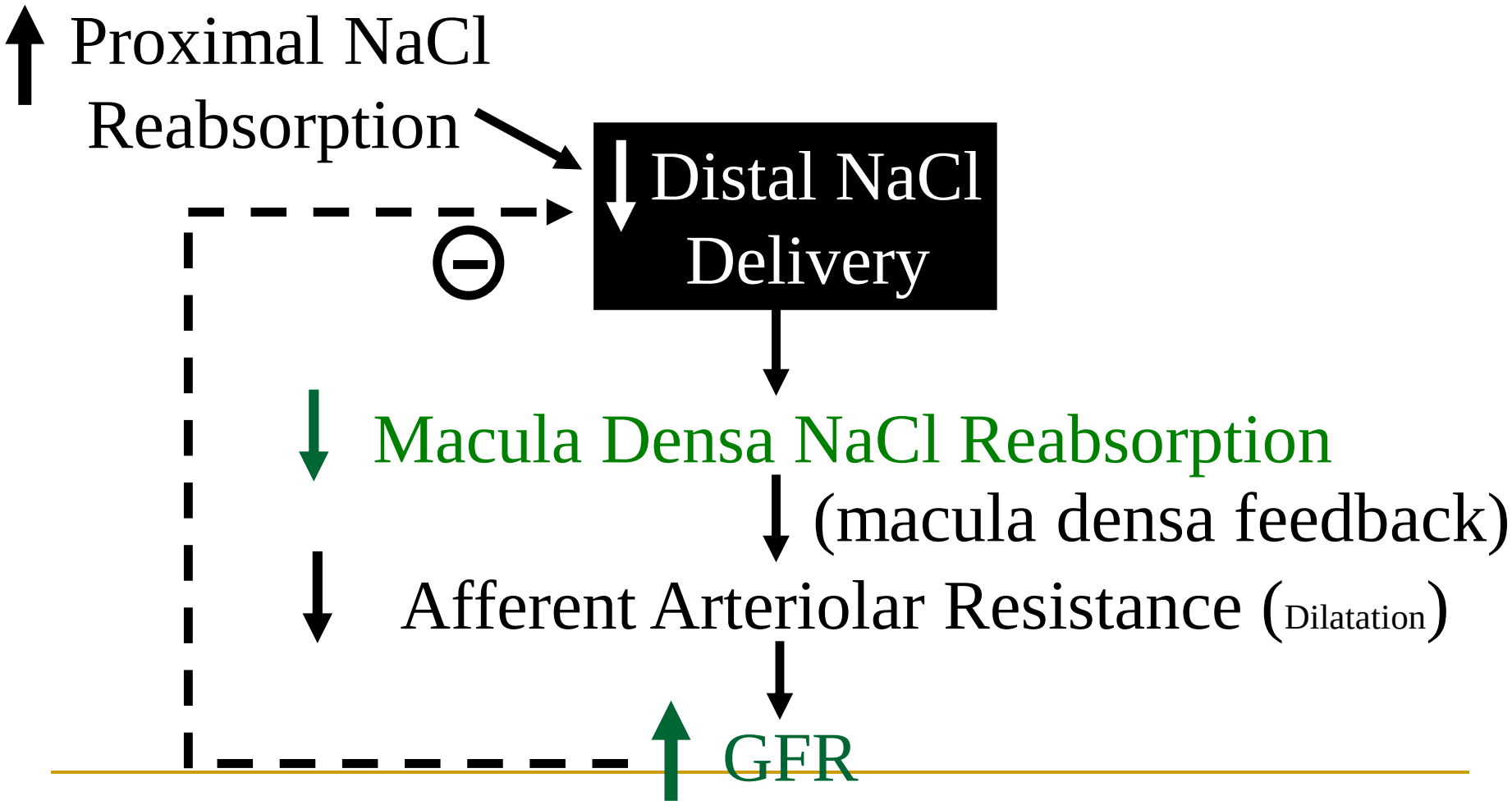
Structure of the juxtaglomerular apparatus: macula densa



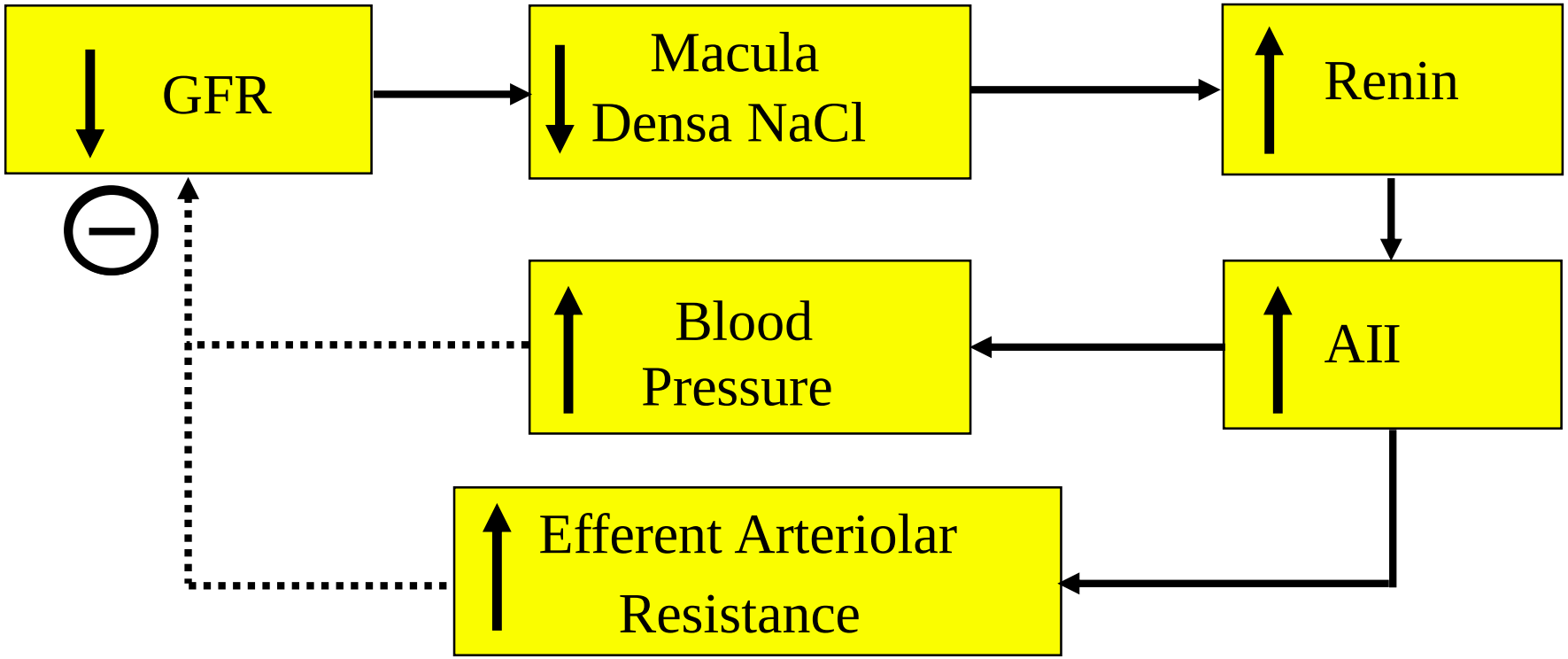
Macula Densa Feedback



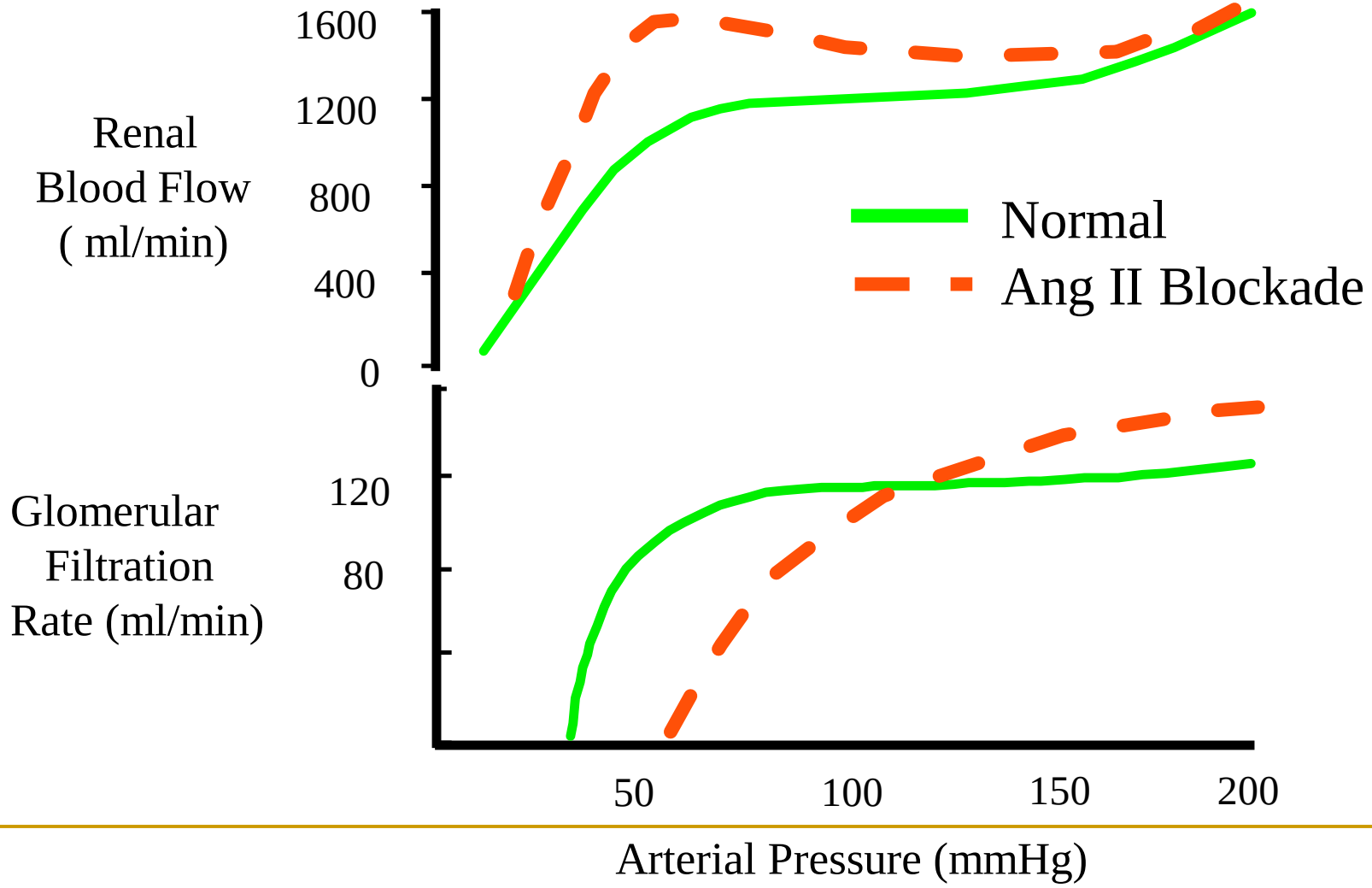
Macula Densa Feedback



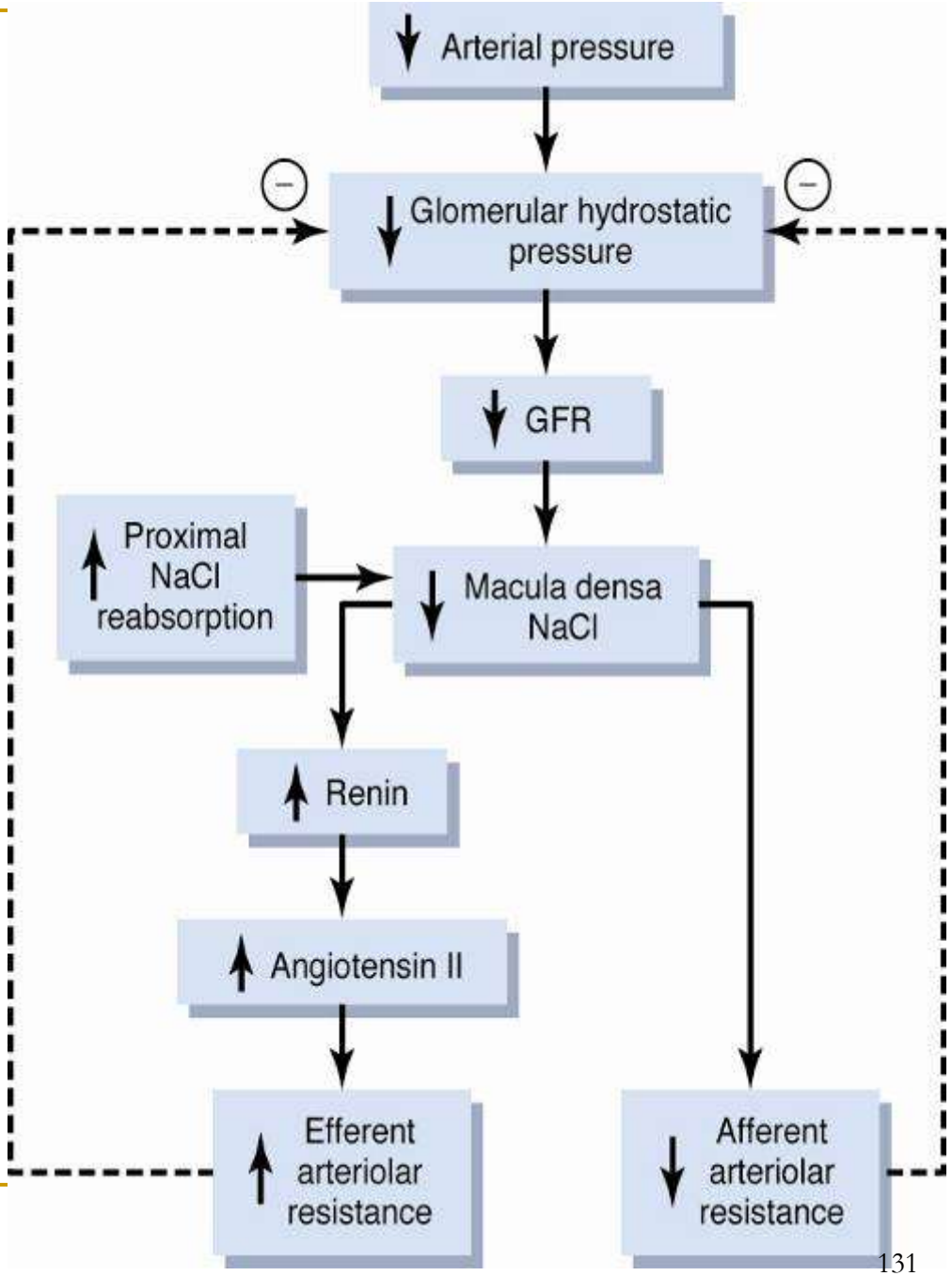
Regulation of GFR by AII



Ang II Blockade Impairs GFR Autoregulation

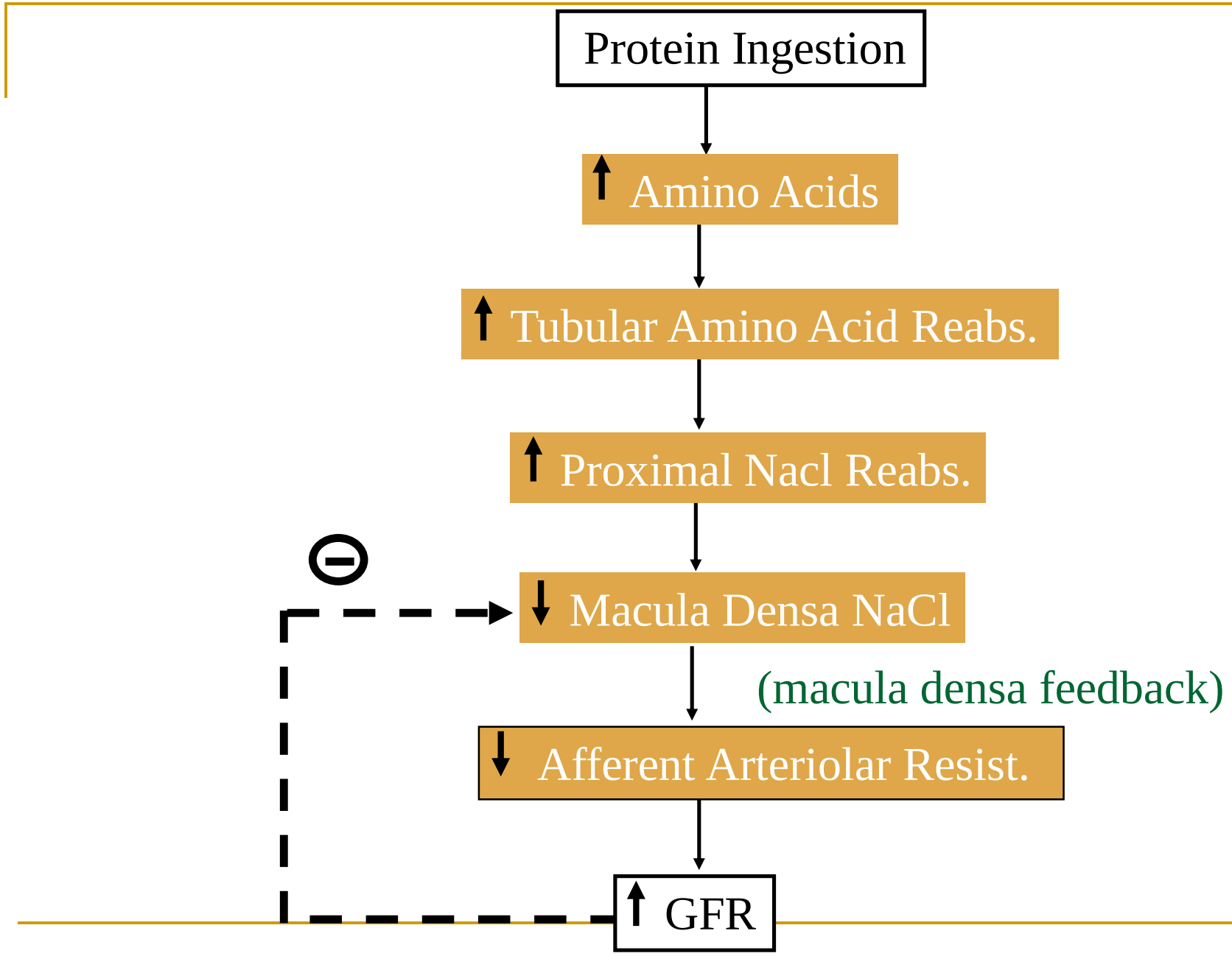


Macula densa feedback mechanism for regulating GFR



Other Factors That Influence GFR

- Fever, pyrogens: increase GFR
- Glucorticoids: increase GFR
- Aging: decreases GFR 10% / decade after 40 yrs
- Hyperglycemia: increases GFR (diabetes mellitus)
- Dietary protein: high protein increases GFR
  low protein decreases GFR


Protein Ingestion
Amino Acids
Tubular Amino Acid Reabs.
Proximal Nacl Reabs.
Macula Densa NaCl
(macula densa feedback)
Afferent Arteriolar Resist.
GFR