RENAL PHYSIOLOGY

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January 10th, 2023

FLUID COMPARTMENTS

FLUID BALANCE

What is the 60-40-20 rule as it pertains to fluid compartments/balance?

60-40-20 RULE

- Total body water is 60% of body weight in animal with normal body condition
    - Higher if emaciated
    - Lower if over-conditioned
  - 2/3 (40% of total BW) is intracellular
  - 1/3 (20% of total BW) is extracellular
    - Further divided into interstitial and plasma volumes
- Movement between intra-extracellular spaces dictated by OSMOTIC PRESSURE
- Movement within extracellular space (interstitial-plasma) is dictated by STARLING'S FORCES

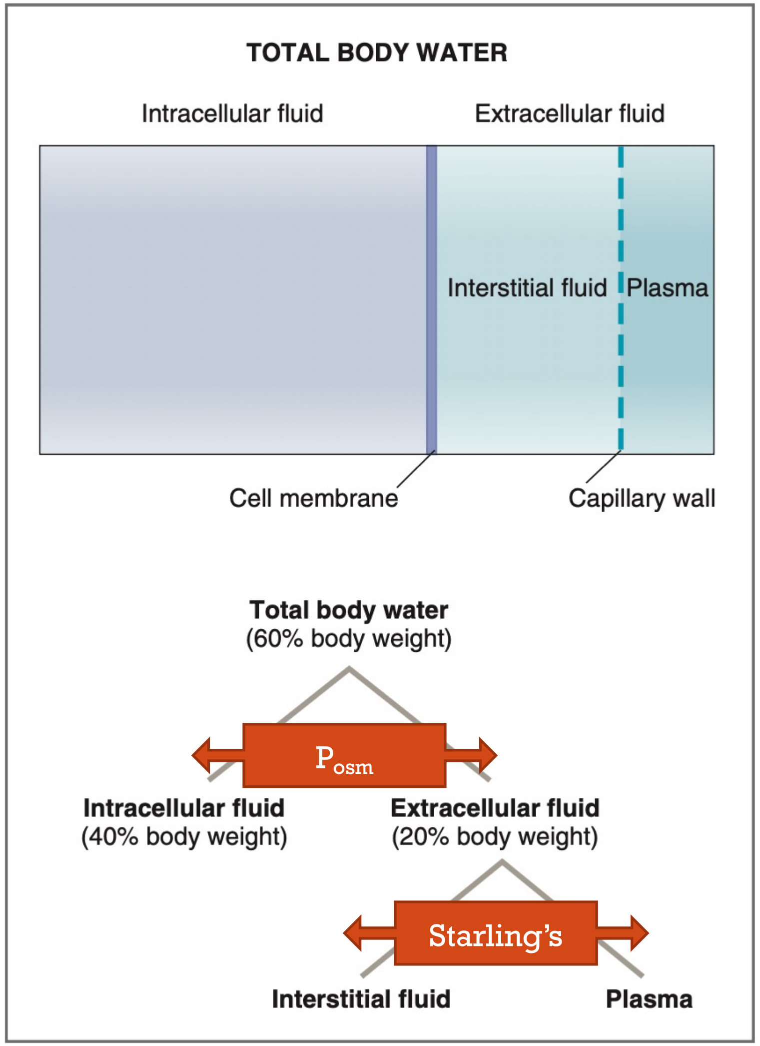


Fig. 6.4 Body fluid compartments. Total body water is distributed between intracellular fluid and extracellular fluid. Water as a percentage of body weight is indicated for the major compartments.

Which of the following volumes can be measured DIRECTLY (i.e NOT calculated values)

- Total body water
- Intracellular volume
- Extracellular volume
- Plasma volume
- Interstitial fluid volume

MEASUREMENT OF FLUID COMPARTMENTS

- Injection of a known volume/concentration of solute with a predictable distribution between compartments
  - Total body water and extracellular water measured directly
  - Intracellular water is calculated value
- Volume can be calculated based on the indicator-dilution principal
  - Total amount of injected substance must remain the same
    - Amount= volume x concentration
    - $V_1C_1 = V_2C_2$
    - $V_1 = V_2C_2/C_1$

Table 25-3 Measurement of Body Fluid Volumes

Volume	Indicators
Total body water	^3H_2O, ^2H_2O, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water – extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = plasma volume/(1 – hematocrit)
Interstitial fluid	(Calculated as extracellular fluid volume – plasma volume)

What is the equation used to calculate P_{osm}? What is the normal osmolarity in companion animal species?

What is the difference between osmolarity and osmolality?

What is the equation for Starling's forces? How has this equation been changed (some might say modified) recently?

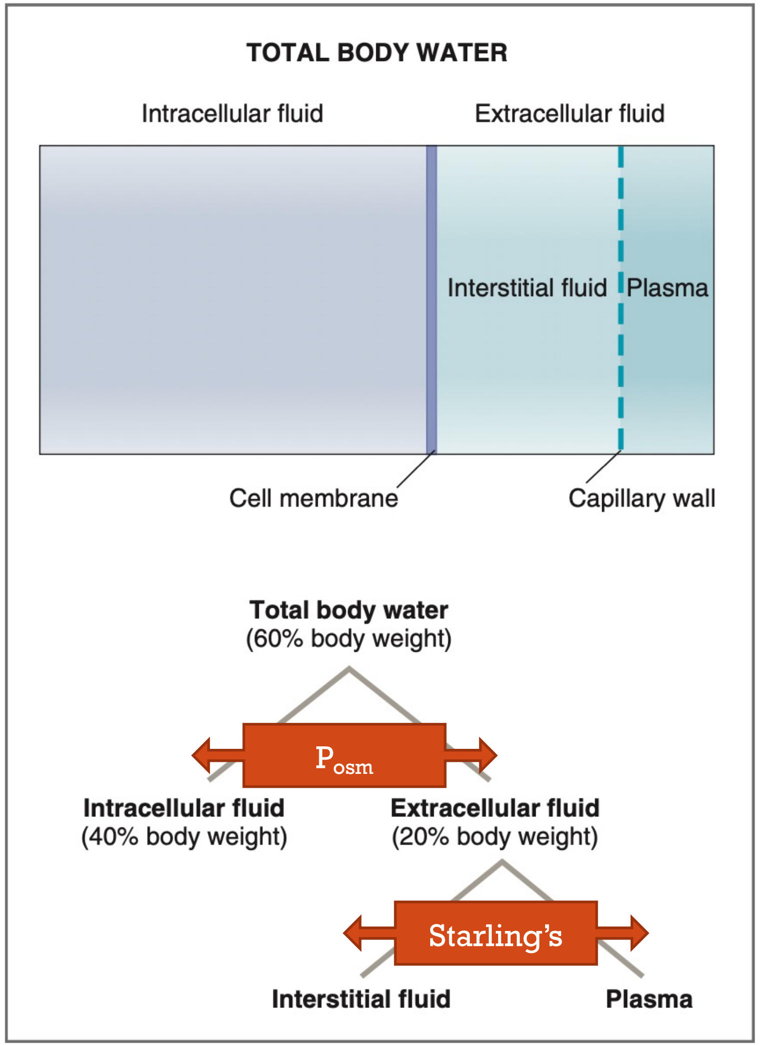


Fig. 6.4 Body fluid compartments. Total body water is distributed between intracellular fluid and extracellular fluid. Water as a percentage of body weight is indicated for the major compartments.

NORMAL FLUID DISTRIBUTION

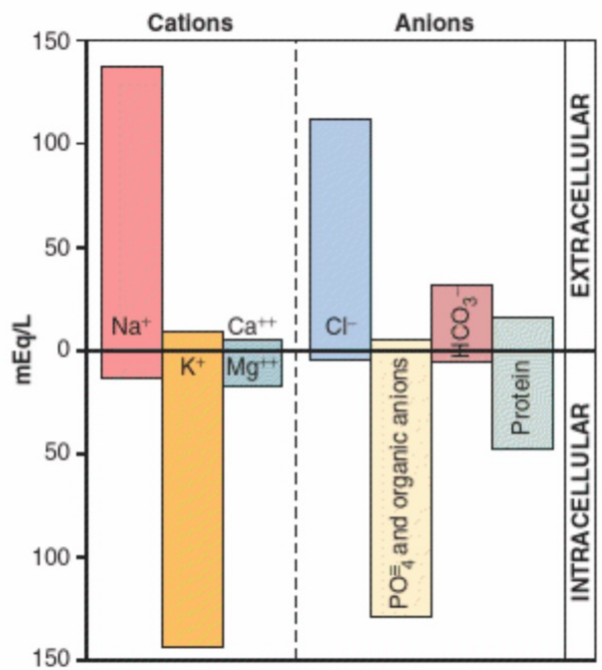
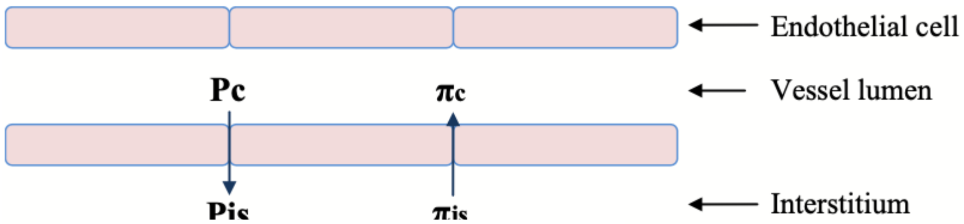


Figure 25-2. Major cations and anions of the intracellular and extracellular fluids. The concentrations of Ca^{++} and Mg^{++} represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions.

- Osmolality: osmoles/kg H_2O
- Osmolarity: osmoles/L H_{2O}
- Osmolarity/osmolality can be used interchangeably because 1kg H_2O=1L H_2O
- Calculated osmolarity (mOsm/L):
  - $2[Na] + \frac{[BUN](mg/dL)}{2.8} + \frac{[BG](mg/dL)}{18}$
  - Normal osmolarity= 300mOsm/L
- △ 1mOsm= 19.3mmHg osmotic pressure

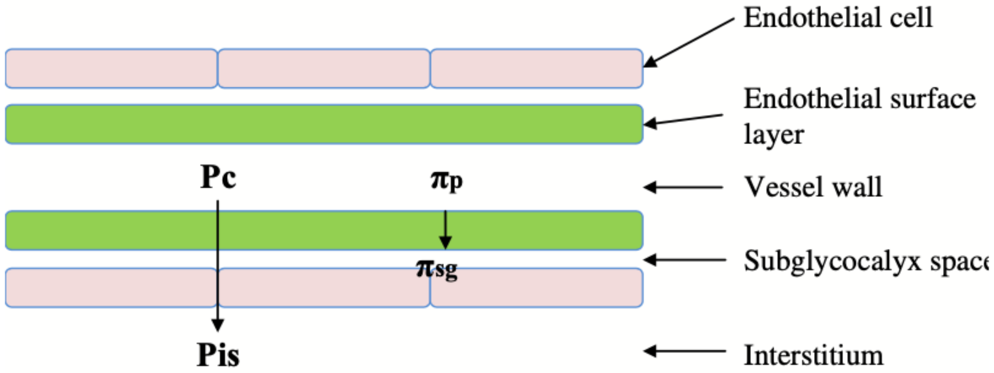
STARLING'S EQUATION

Classic Starling's equation



$$J = K(P_c - P_{is}) - \sigma(\pi_c - \pi_{is})$$

Modified Starling's equation



$$J = K(P_c - P_{is}) - \sigma(\pi_c - \pi_{sg})$$

P  π

RENAL ANATOMY AND BLOOD FLOW

GROSS ANATOMY

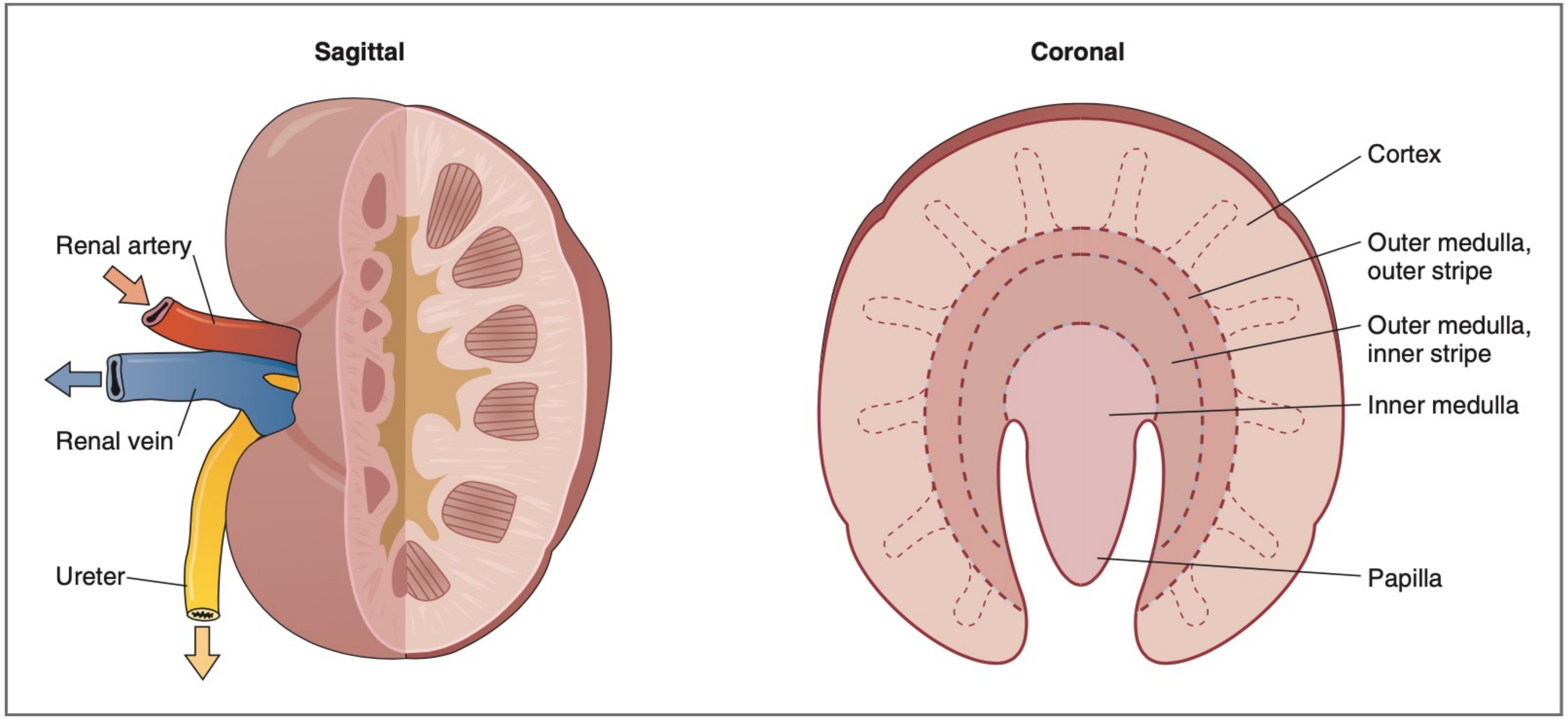


Fig. 6.1 Sagittal and coronal sections of the kidney.

RENAL BLOOD FLOW

What is the typical course of blood as it flows through the kidney? How does the organization of renal vasculature differ from that of other organs?

What is the equation for flow?

What renal vessels have the greatest degree of resistance (and thus cause the largest changes in pressure?)

RENAL BLOOD FLOW

- Blood Flow
  - Renal a. → interlobar a. → arcuate a → interlobular (radial) a. → afferent arterioles → **glomerular capillary** → efferent arterioles → **peritubular capillaries** →interlobular v. →arcuate v. → interlobar v. → renal v.

Important to remember that the kidneys have TWO sets of capillaries and TWO sets of arterioles

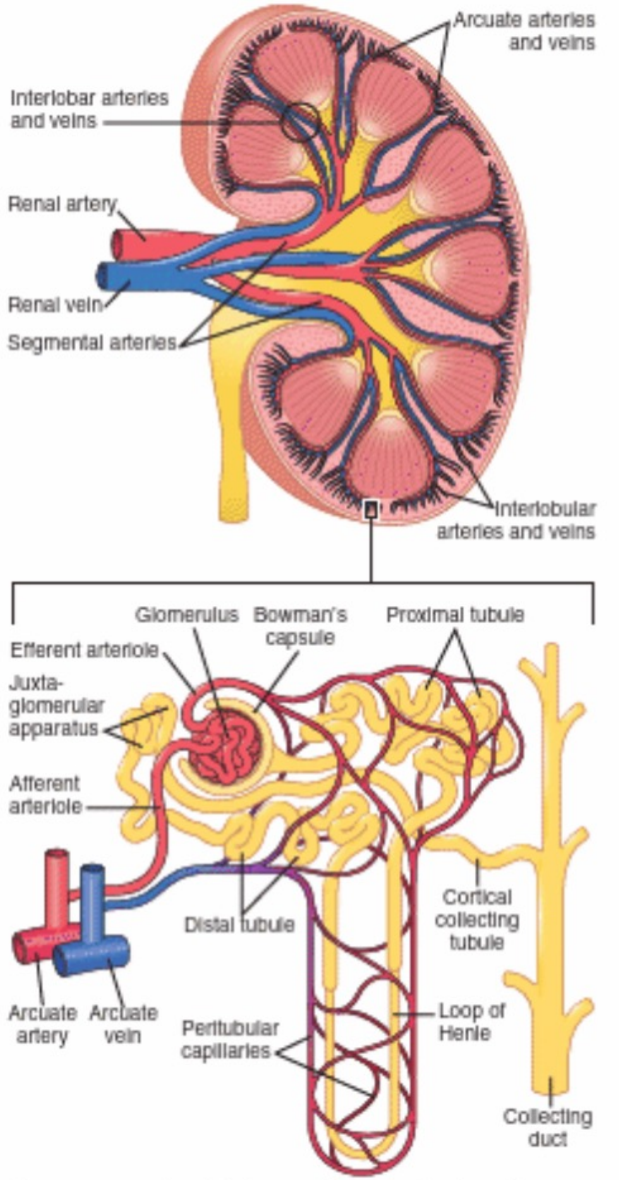
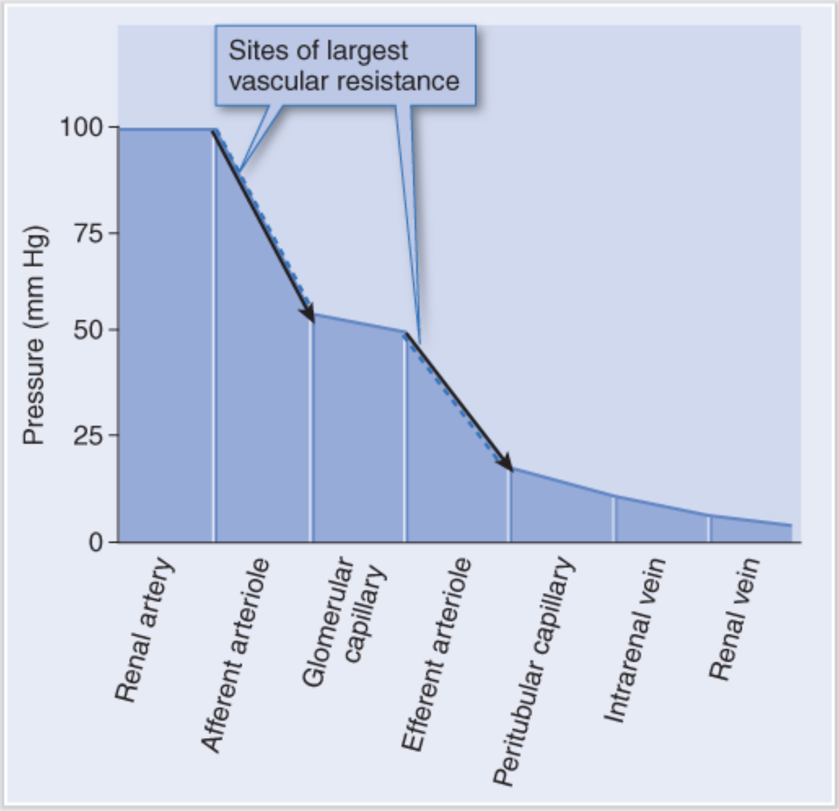


Figure 26-3. Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the micro-circulation of each nephron.

RENAL VASCULAR PRESSURES/RESISTANCE

- Q= ΔP/R
  - Q= follow
  - ΔP= change in pressure
  - R= Resistance
  - Vessels with the largest resistance will have the least flow
- The arterioles (afferent and efferent are the sites of the largest vascular resistance



Source: Eaton DC, Pooler JP: *Vander's Renal Physiology*, Eighth Edition: www.accessmedicine.com

THE NEPHRON:
THE FUNCTIONAL UNIT OF THE KIDNEY

Cortical nephrons

- Glomerulus located in the OUTTER COREX
- Tubules extend into superficial medulla
- Tubular system surrounded by peritubular capillaries

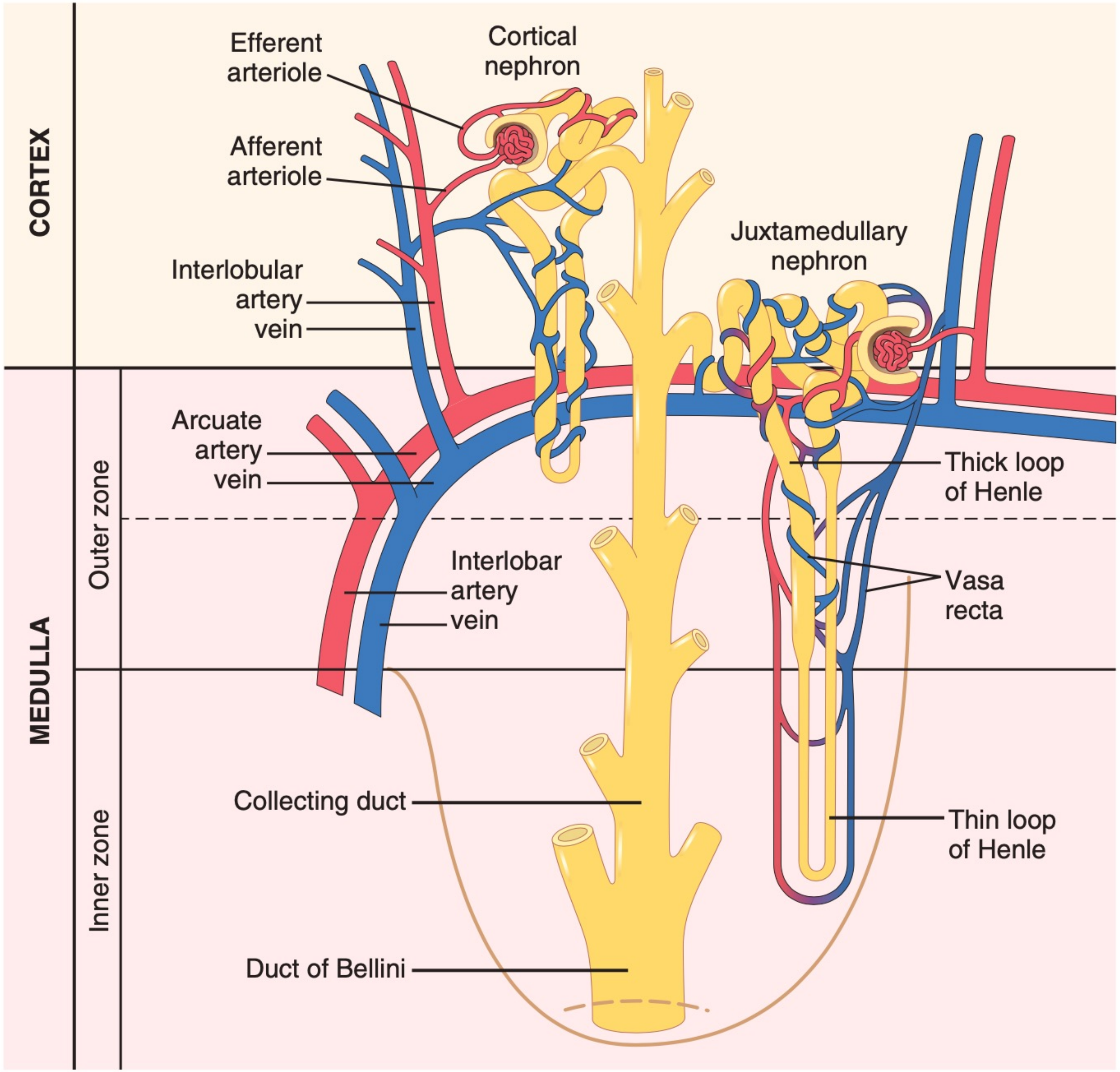
Juxtaglomerular nephrons

- Glomerulus at the INNER CORTEX
- Tubules extend into deep medulla
  - Increased concentrating ability
- Tubular system surrounded by specialized peritubular capillaries called the **vasa recta**

THE N

Cortical ne

- Glomerulı COREX
- Tubules e: medulla
- Tubular sy peritubula



s

CORTEX
medulla
bility
d by
pillaries

THE GLOMERULUS

THE GLOMERULUS

- Glomerular capillary has THREE (3) layers: thicker than most other capillaries
  - Fenestrated endothelium
  - Basement membrane (negative charge)
  - Epithelium (podocytes)

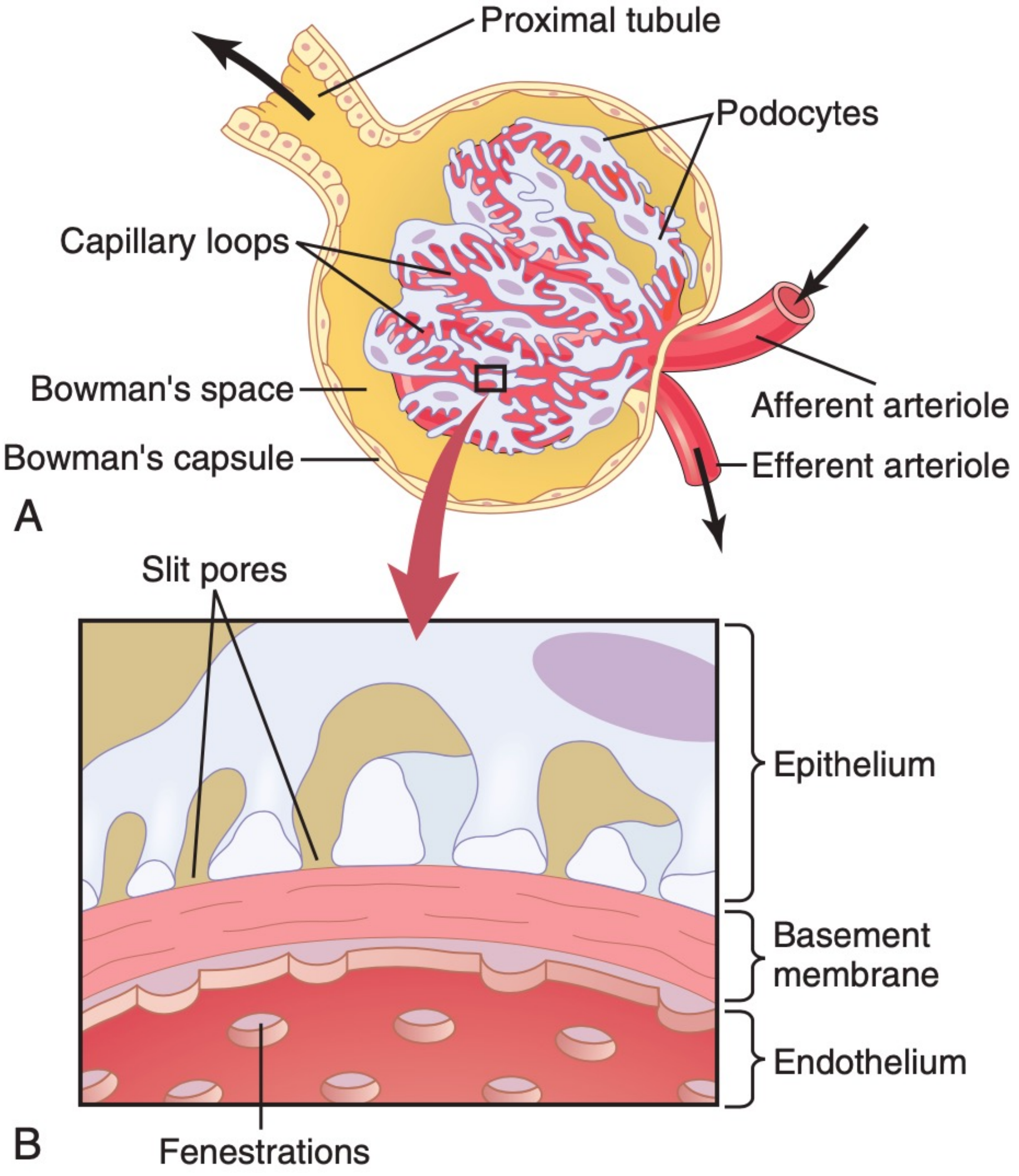


Figure 27-2. A, Basic ultrastructure of the glomerular capillaries. **B,** Cross section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).

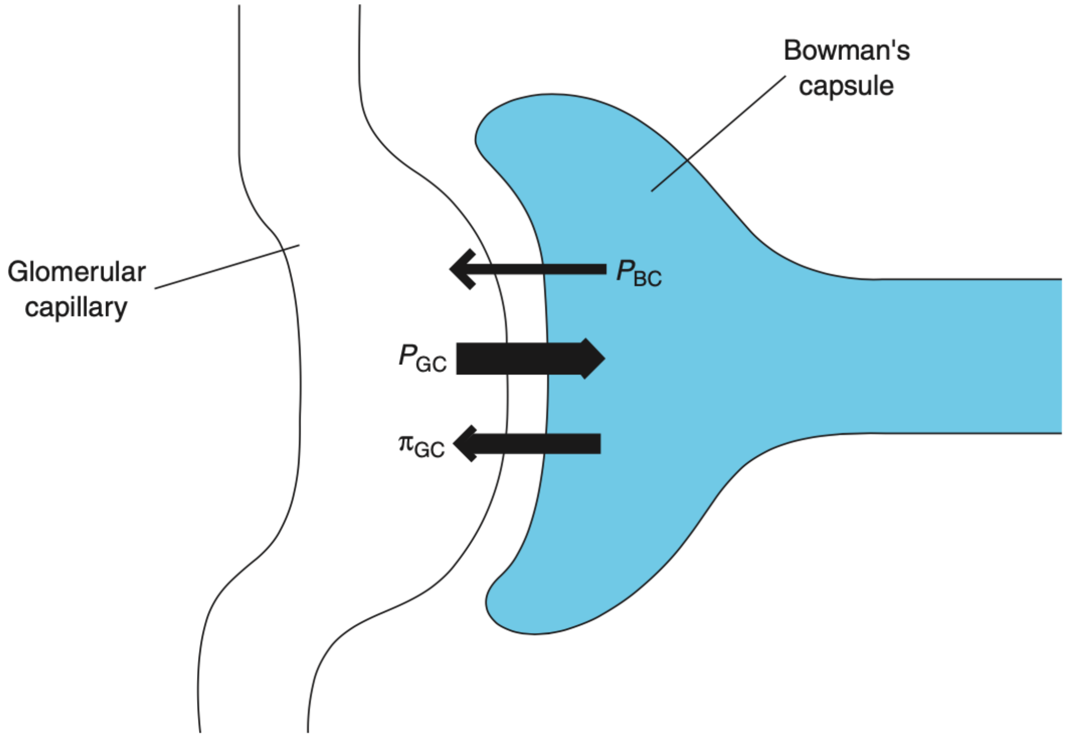
DETERMINING GLOMERULAR FILTRATION RATE (GFR)

What three (3) factors determine the rate of filtration? What is the name the coefficient used to summarize/combine several of these factors?

What is the Starling equation as it relates to glomerular permeability?

GLOMERULAR FILTRATION RATE (GFR)

- Rate of filtration
    - Hydraulic permeability
    - Surface area
    - Net filtration pressure
  - Permeability and surface area combined to create filtration coefficient (K_f)
    - Glomerular capillaries more leaky than most other capillaries (higher K_f)
- Net filtration pressure (NFP)
  - NFP= $(P_{GC} - \pi_{GC}) - (P_{BC} -$ ~~π_{BC})~~
- **Glomerular Filtration Rate (GFR)**
  - **$GFR = K_f\,(P_{GC} - P_{BC} - \pi_{GC})$**



P_{GC} under physiologic control

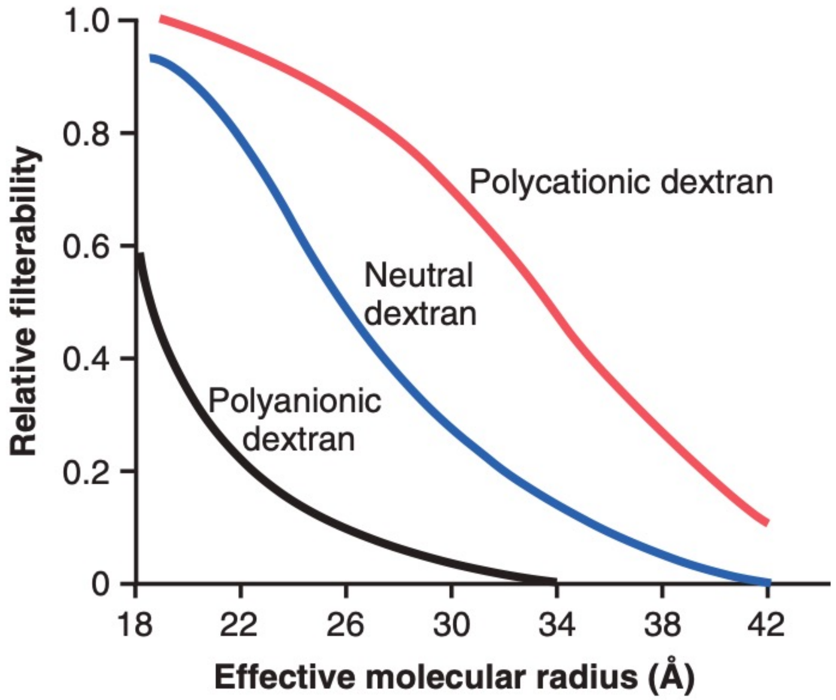
- Remainder of variables primarily influenced by disease states

Which of the following subsances will be most easily filtered at the level of the glomerulus?

- Large, positively charged
- Small, positively charged
- Large, negatively charged
- Small, negatively charged
- Small, neutrally charged
- None of the above

GLOMERULAR PERMEABILITY

- Selective permeability based on size and charge
  - Excludes LARGE, NEGATIVELY CHARGED substances
    - Substances </=7,000 Da move freely
      - (ex: albumin=66,000 Da)
    - Negative charge of basement membrane repels negatively-charged substances



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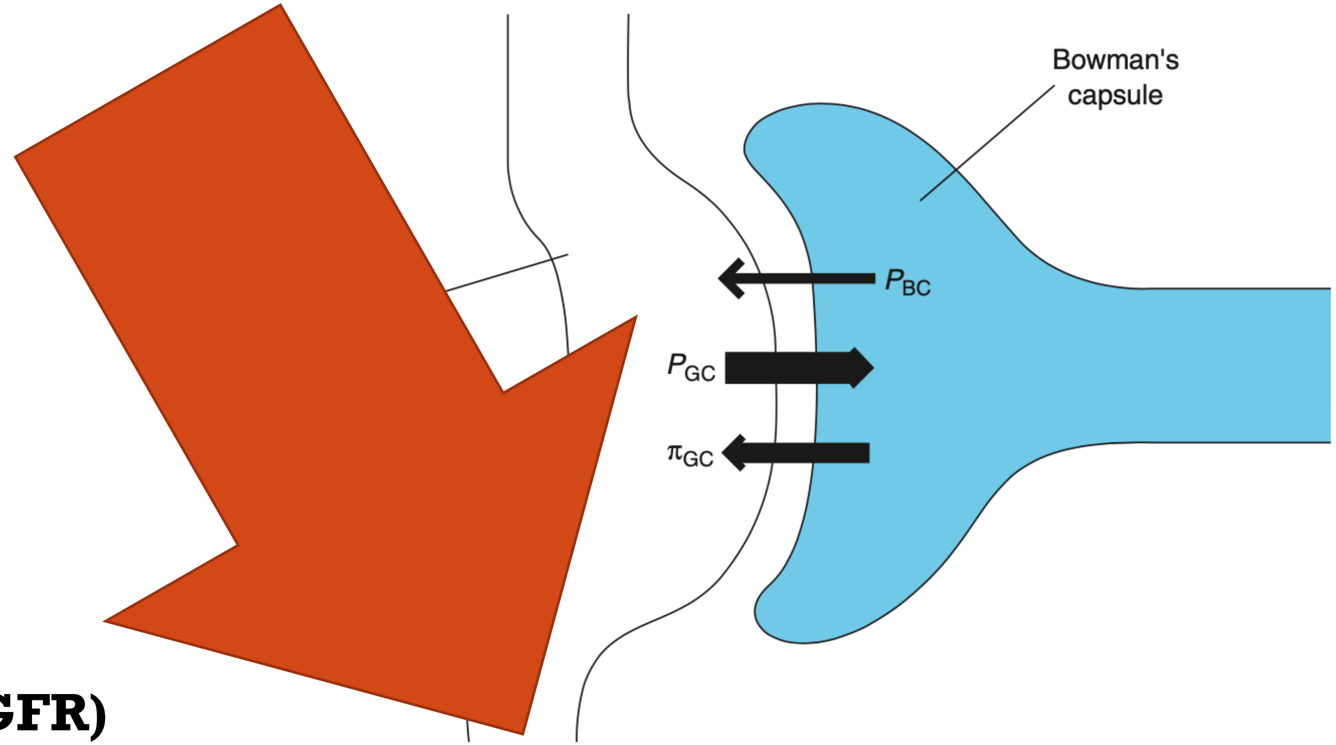
  - NFP= $(P_{GC} - \pi_{GC}) - (P_{BC} -$ ~~$\pi_{BC})$~~
- **Glomerular Filtration Rate (GFR)**
  - **GFR = $K_f (P_{GC} - P_{BC} - \pi_{GC})$**



P_{GC} under physiologic control

- Remainder of variables primarily influenced by disease states

GLOMERULAR CAPILLARY HYDROSTATIC PRESSURE (P_{GC}) AND GFR

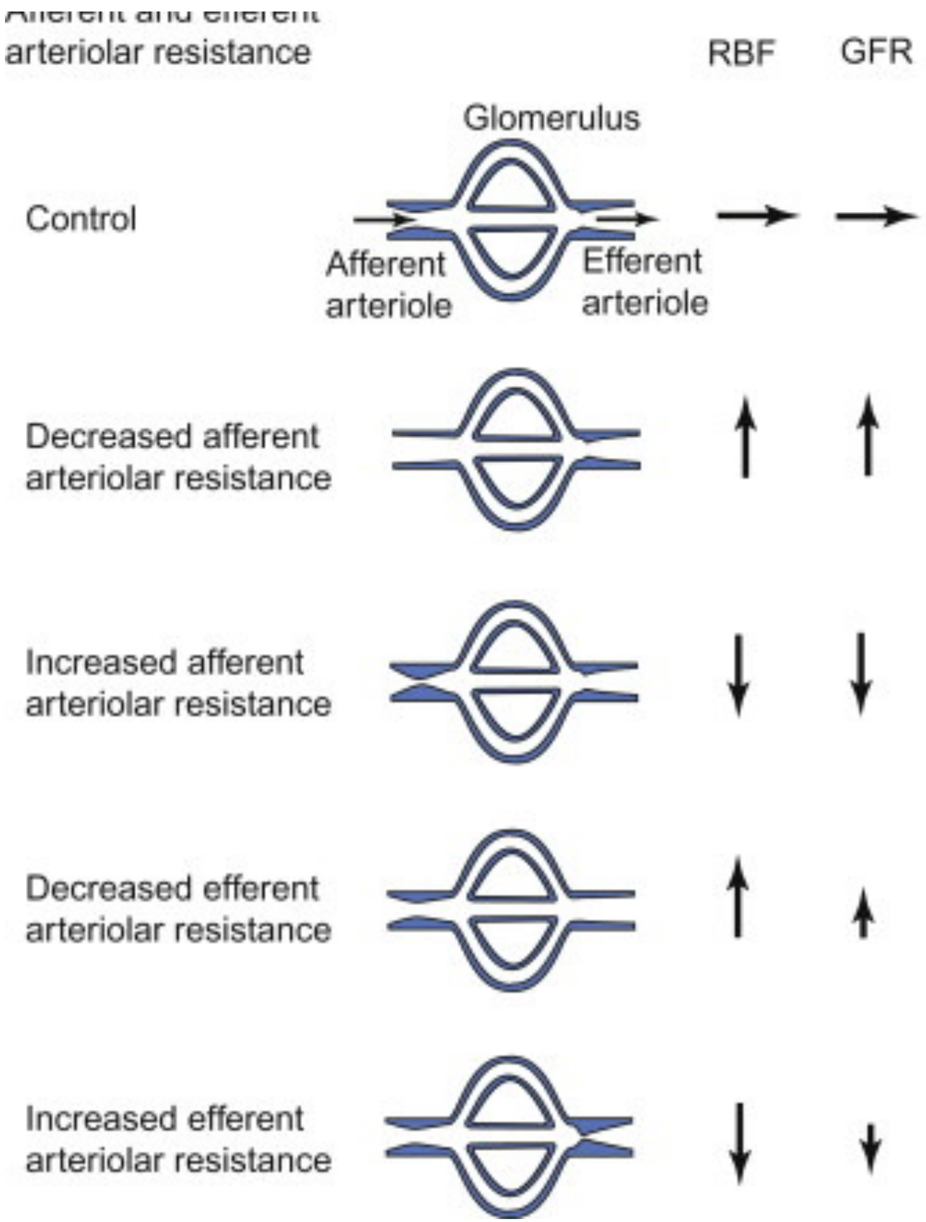
GLOMERULAR CAPILLARY HYDROSTATIC PRESSURE (P_{GC})

Describe 3 different mechanisms of increasing P_{GC}

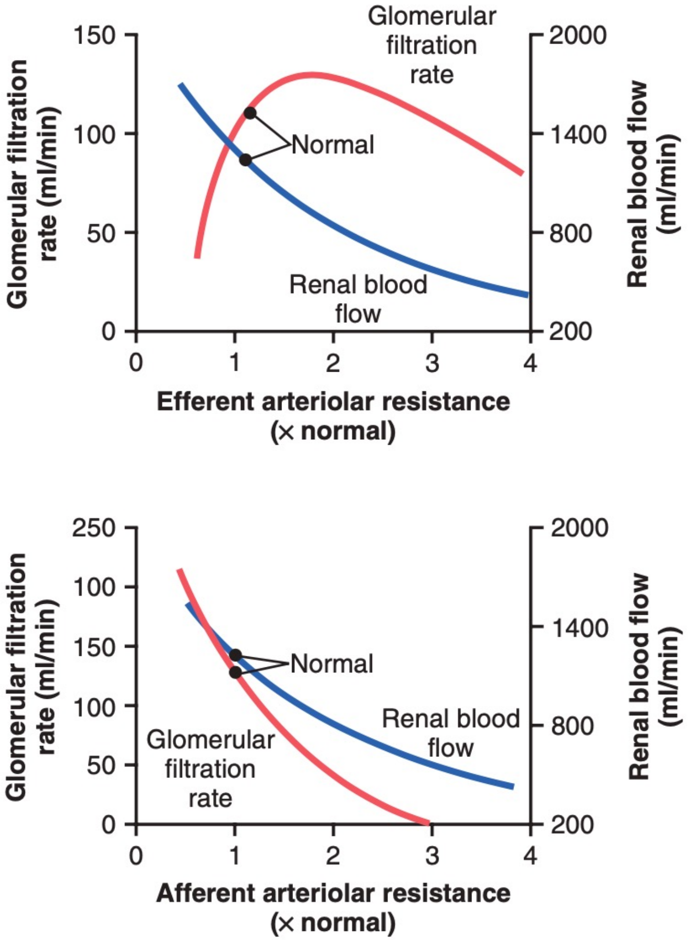
Describe autoregulation and what mechanisms (2) contribute to this phenomenon

REGULATION OF P_{GC}

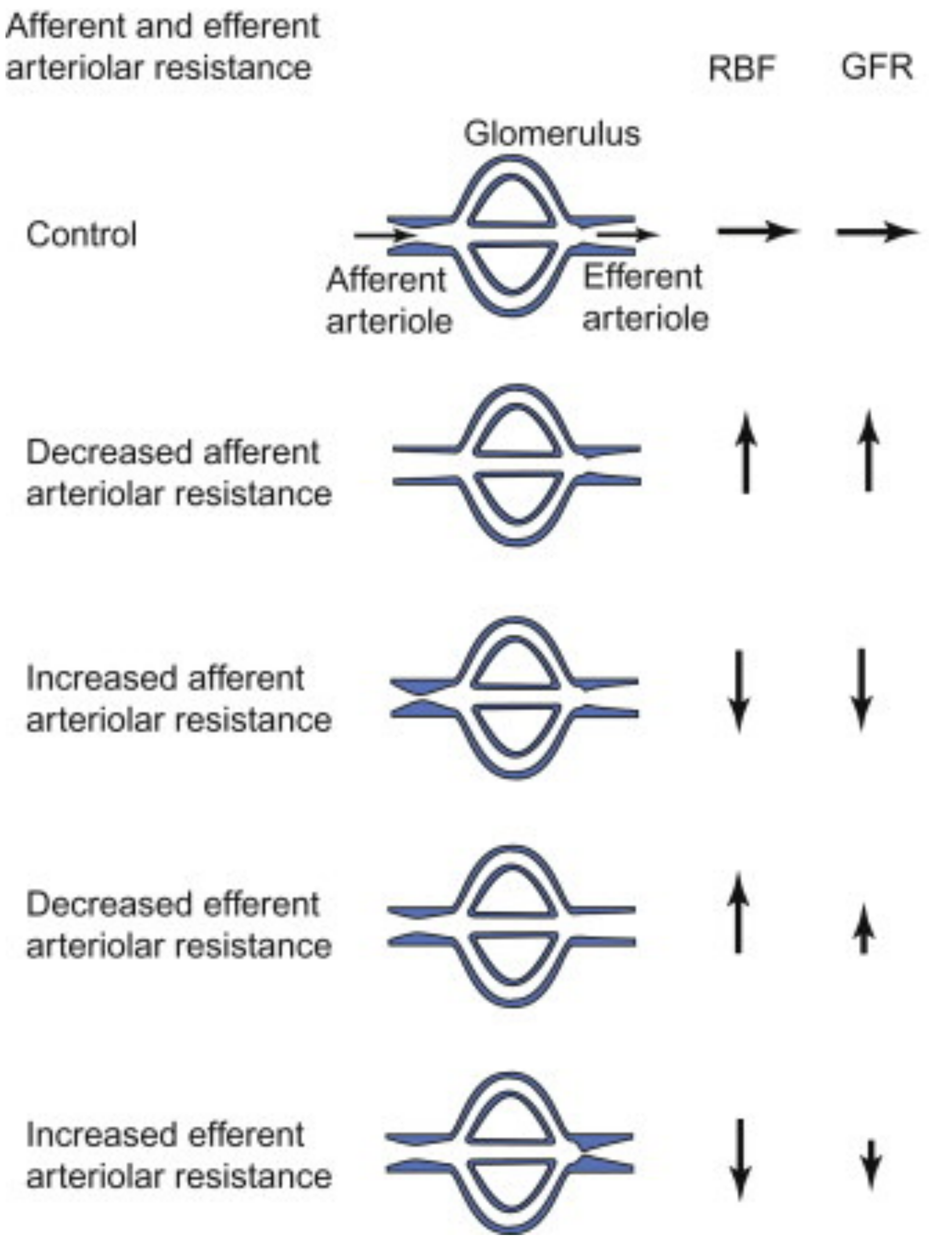
- Myogentic regulation of P_{gc} determined by three (3) variables
  - Renal arterial pressure
  - Afferent arteriolar resistance
  - Efferent arteriolar resistance



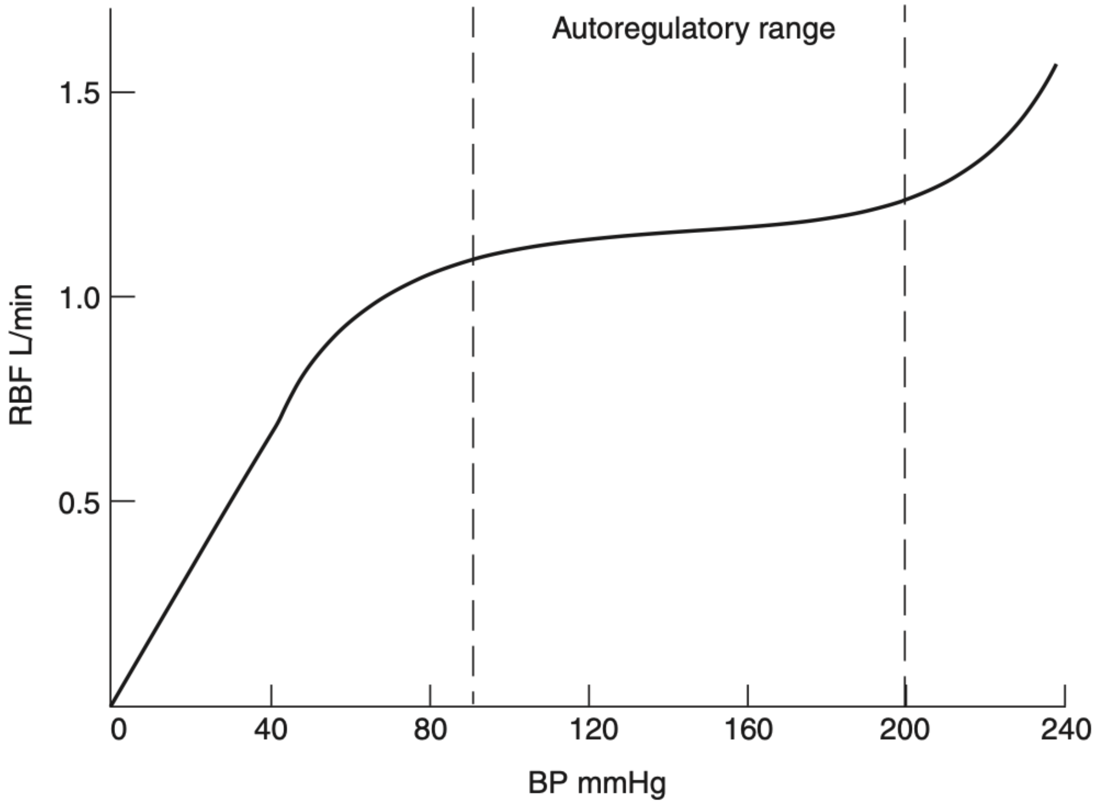
REGULATION OF P_{GC}



Donnan effect



AUTOREGULATION: CONTROL OF P_{GC}



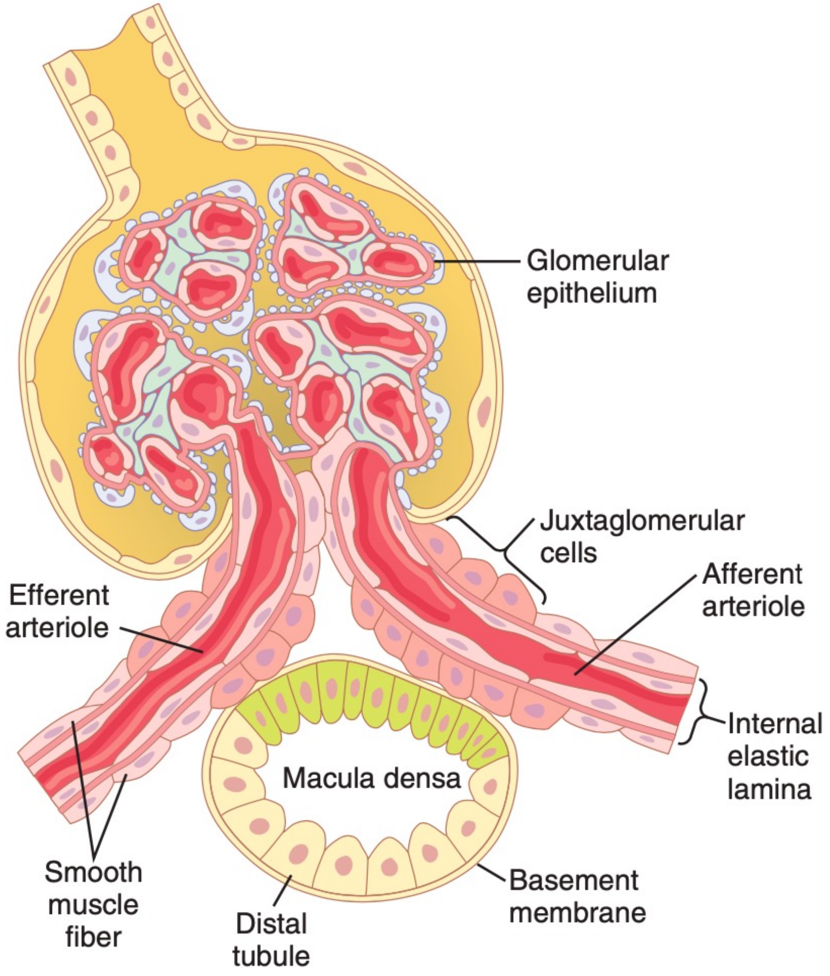
- Changes in MAP cause only small changes in GFR within physiologic range
  - Caused by two different mechanisms
    - 1. **Myogenic response:** Fast response by stretch of smooth muscle at the level of the arteriole
    - 2. **Tubuloglomerular feedback:** Slower response by Δ[Na] at the level of the macula densa (RBF)

Which of the following substances preferentially constricts the efferent arteriole?

- Epinephrine/Norephinephrine
- Nitric Oxide
- Angiotensin II
- Prostaglandins
- Endothelin
- None of the above

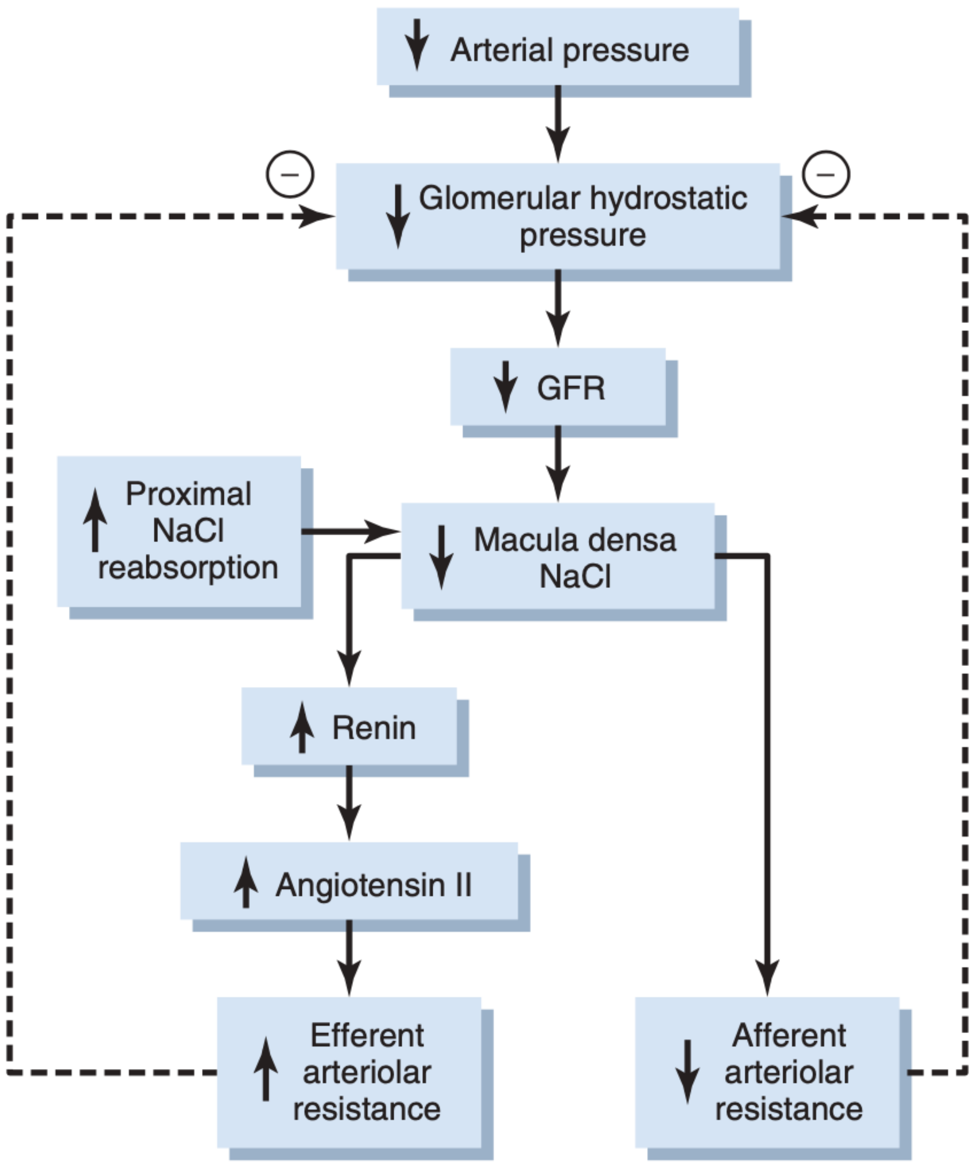
REGULATION OF P_{GC}

- Tubuloglomerular feedback occurs at the level of the juxtaglomerular apparatus
  - Point of contact of the distal tubule and afferent/efferent arterioles
  - Macula densa detects [Na] ([Cl])



REGULATION OF P_{GC}

- Tubuloglomerular feedback occurs at the level of the juxtaglomerular apparatus
  - Point of contact of the distal tubule and afferent/efferent arterioles
  - Macula densa detects [Na]
    - Decreased [Na] interpreted as reduced GFR
      - DILATION of the AFFERENT arteriole
        - PG and NO
      - CONSTRICTION of EFFERENT arteriole
        - AgII



MEASUREMENT OF GFR AND CLEARANCE

Describe the renal handling of a substance used to measure GFR. What substance is used for this purpose?

What is the definition of clearance? What are the units for this measurement?

MEASURING GFR

- Urinary excretion rate=

filtration rate – reablank sorption rate + secretion rate

- **Ideal substance for measuring GFR is freely filtered but NOT reabsorbed or secreted**
  - Inulin is the gold standard
  - Creatinine used clinically because it is produced at a steady state in the body
    - Small component of secretion → slightly **overestimates** GFR

Received: 23 December 2020 | Accepted: 19 January 2022
DOI: 10.1111/jvim.16377

REVIEW

Journal of Veterinary Internal Medicine
Open Access
ACVIM
American College of Veterinary Internal Medicine

Renal biomarkers in cats: A review of the current status in chronic kidney disease

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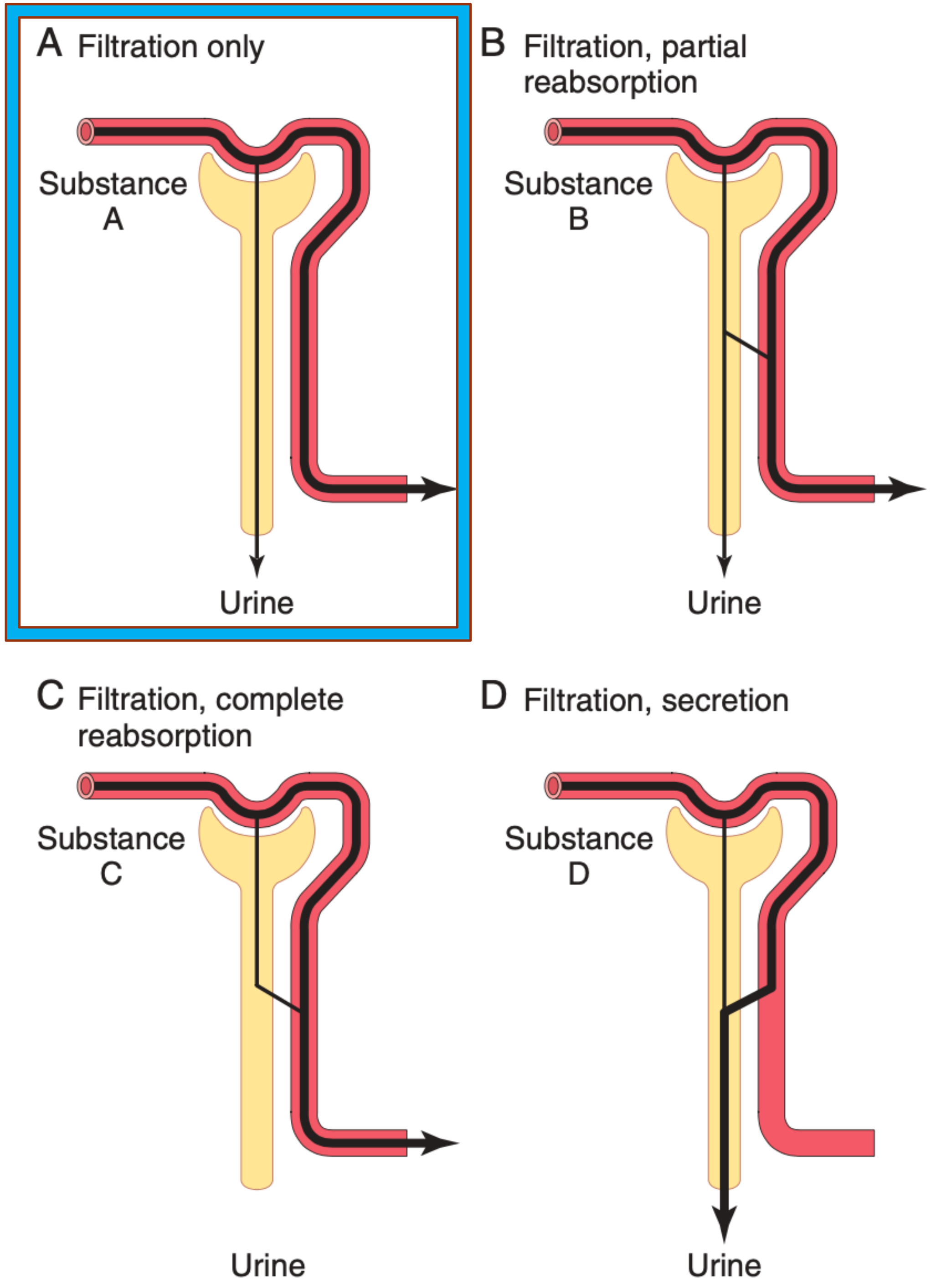
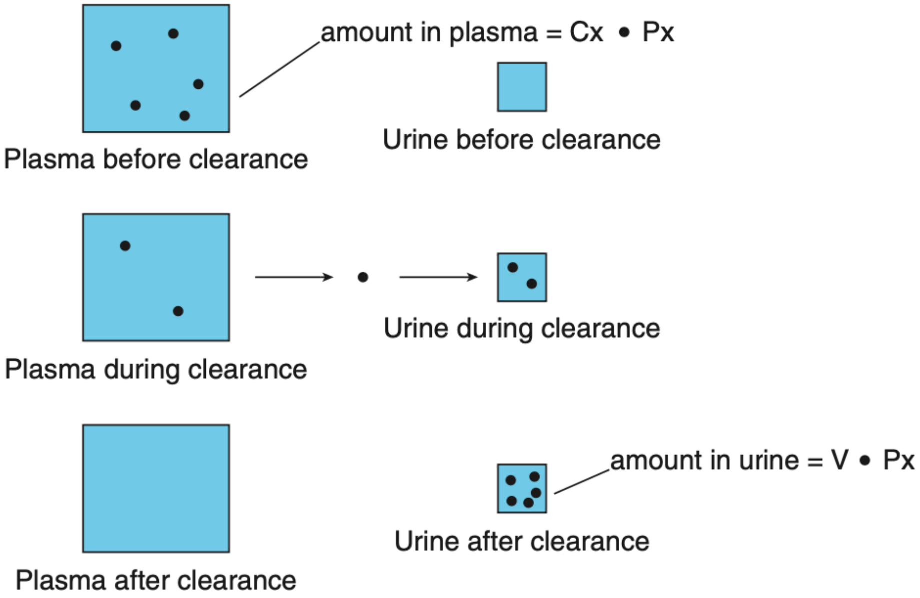


CLEARANCE AND EXCRETION

- Excretion rate:
  - AMOUNT of substance removed per unit time
- Clearance:
  - VOLUME of plasma from which a substance is removed per unit time

$\text{Clearance}_X = \text{excretion}_X / [X_{plasma}]$

$$\text{Renal clearance} = \frac{\text{Urine flow x } [X_{urine}]}{[X_{plasma}]}$$



amount in plasma = amount in urine (3-1)

$$Cx \bullet Px = V \bullet Ux \quad (3\text{-}2)$$

$$Cx = \frac{V \bullet Ux}{Px} \quad (3\text{-}3)$$

RENAL CLEARANCE

Over a 10 hour period, a large dog produces 0.6L of urine. The concentration of sodium in the urine is 200mmol/L and the dog's blood sodium is 140mmol/L. What is the renal clearance of sodium?

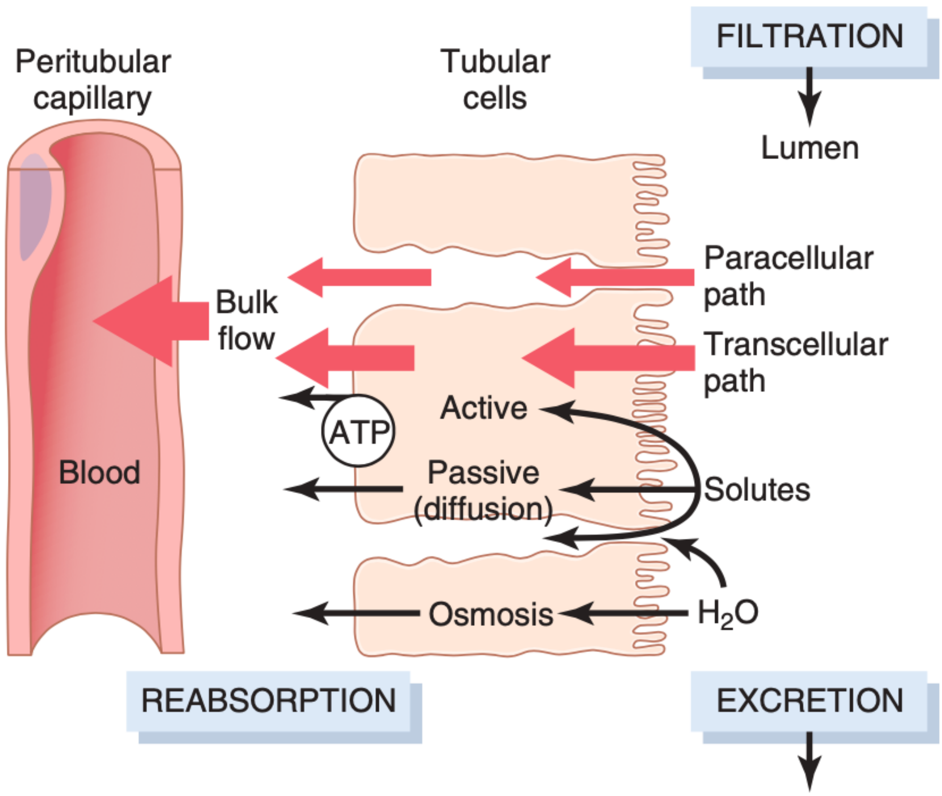
- **Renal clearance=** $\dfrac{\textbf{Urine flow x [Xurine]}}{[X_{plasma}]}$

RENAL CLEARANCE

- **Renal clearance=** $\frac{\textbf{Urine flow x [Urinex]}}{\textbf{[Plasma}_x\textbf{]}}$
  - Urine flow = $\frac{0.6L}{10h} = \frac{0.06L}{h}$ x $\frac{1h}{60min} = \frac{0.001L}{min}$
  - $[Urine_{Na}]$= 200mmol/L
  - $[Plasma_{Na}]$= 140mmol/L
- $\frac{\frac{0.001L}{min} x \frac{200mmol}{L}}{\frac{140mmol}{L}}$
- 0.0014L/min= 1.42mL/min

TRANSPORT MECHANISMS

MECHANISMS OF REABSORPTION



- Solutes
  - Can be absorbed passively or actively
    - Passive transport: WITH electrochemical gradient
      - Tight junctions (Paracellular)
      - Channels (transcellular)
    - Active transport: AGAINST electrochemical gradient using transporters (transcellular)
      - Primary: Uses ATP as energy source
      - Secondary: Uses energy generated from another substance moving via passive transport
        - Uniporter
        - Antiporter/exchanger
- Water
  - Always absorbed passively (osmosis)

What antiporter is the major energy driver for secondary active transport?

Tubular reabsorption can be limited via two different mechanisms. What are these limiting steps and what property of the tubules/absorbed substance determines the type of threshold/limit?

TRANSPORT THRESHOLDS

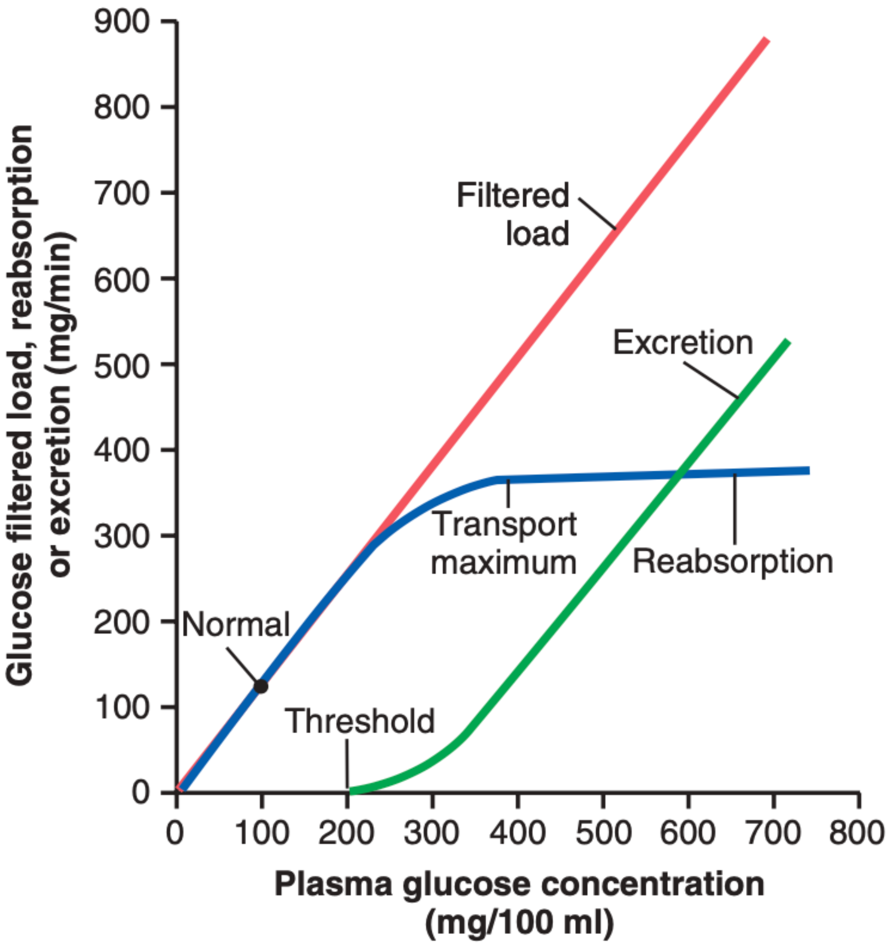
Gradient-limited

- Amount of substance transported depends on its concentration gradient and amount of time in the tubule
- Tight junctions **leaky** to a substance
  - Ex: Sodium

Tubular maximum: T_m

- Limited active transport of a substance due to saturation of transport systems
- Tight junctions **impermeable** to substance
  - Ex: Glucose, creatinine, phosphate, urates, lactate

TUBULAR MAXIMUM THRESHOLDS

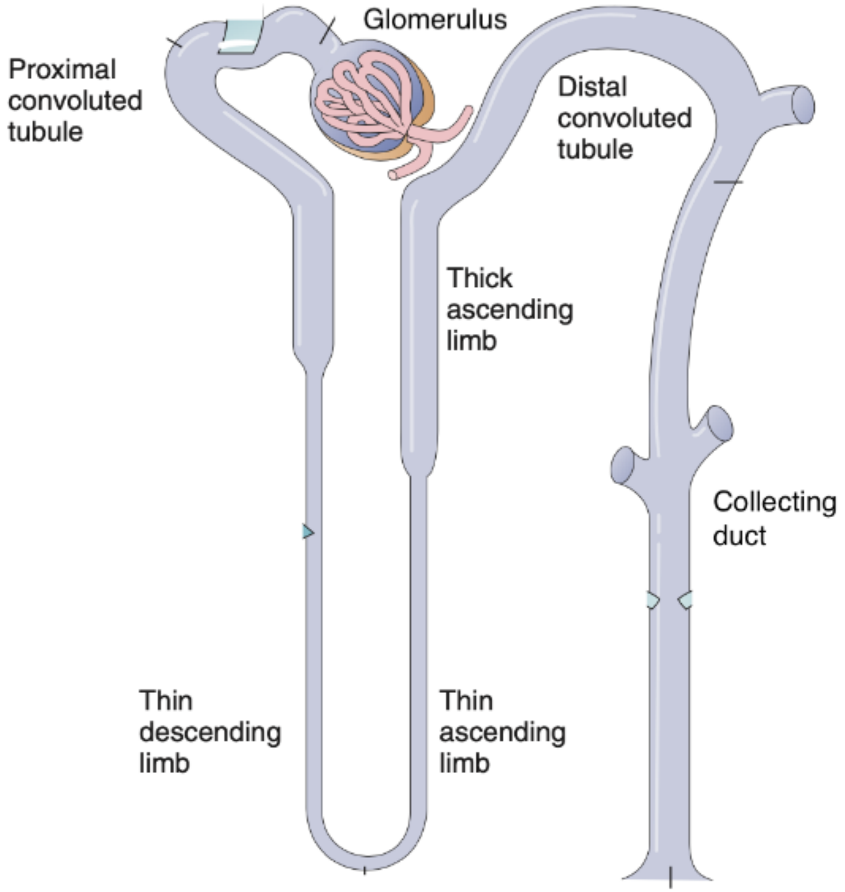


Glucose renal thresholds

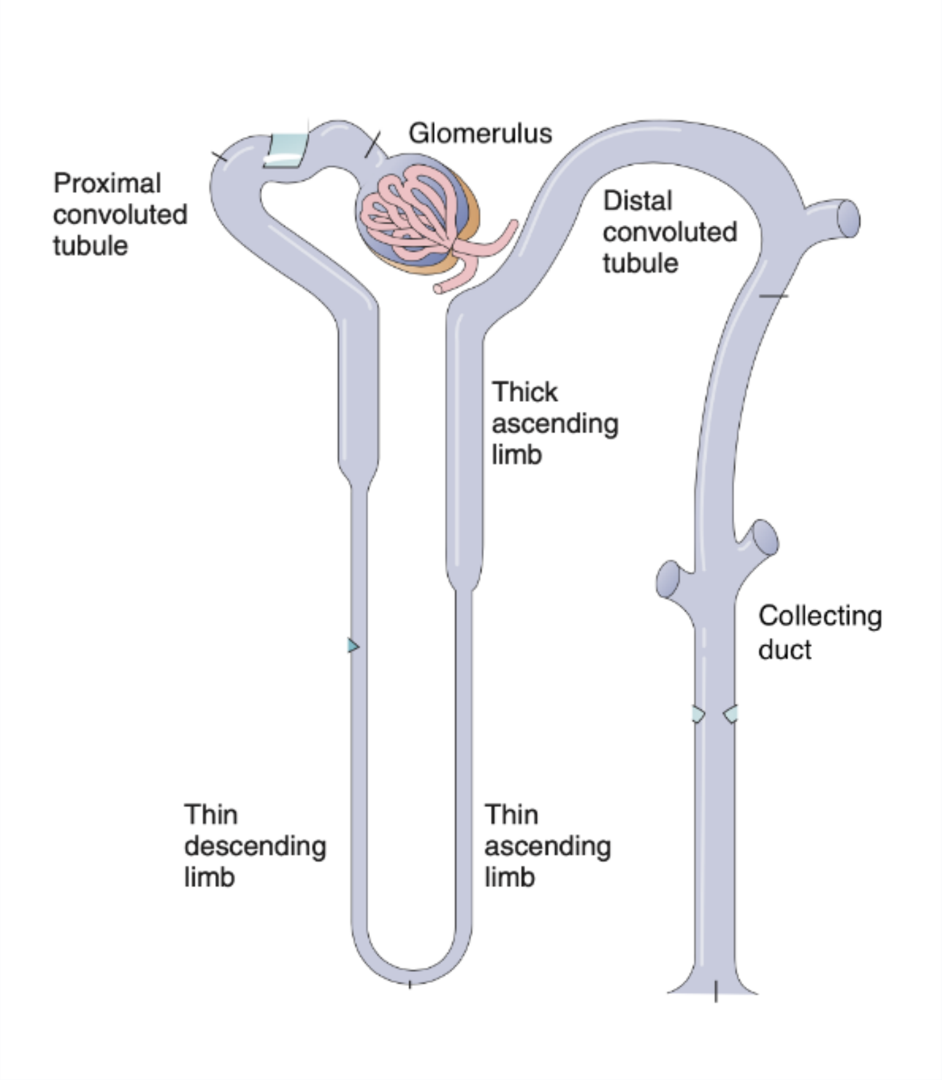
- Dogs
  - 180-200mg/dL
- Cats
  - 280-290mg/dL

DIURETICS

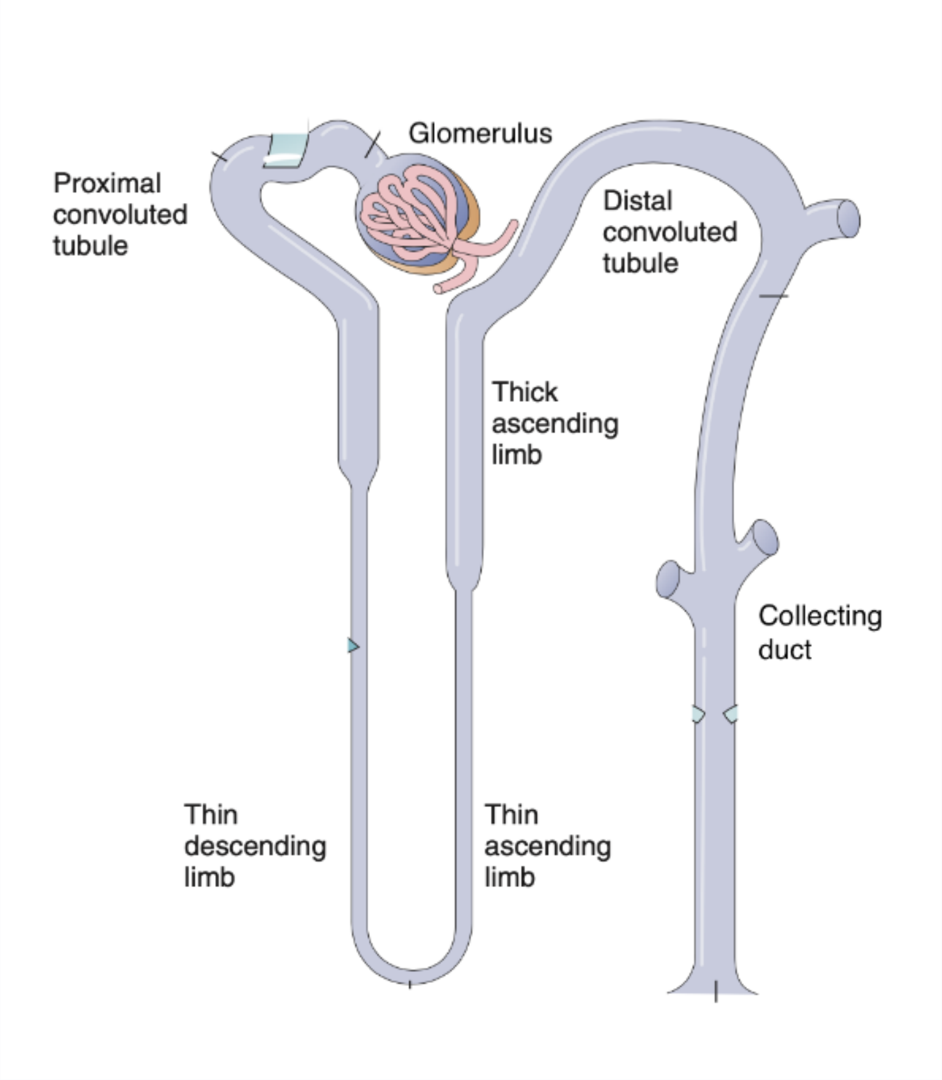
What portion of the nephron do loop diuretics act on?



What portion of the nephron do osmotic diuretics act on?



What portion of the nephron do thiazide diuretics act on?



REVIEW OF DIURETICS

Diuretic	Example	Site of action	Mechanism of Action
Osmotic Diuretic	Mannitol	Proximal tubule	Increased osmolarity resulting in increased Na backleak
Loop diuretic	Furosemide	Thick ascending LoH	Blocks Cl site of NaK2Cl transporter
Thiazide diuretic	Hydrochlorothiazide	Distal tubule	Blocks Cl site of NaCl transporter
K-Sparing diuretic	Spirinolactone	Collecting ducts	Prevents aldosterone action on principal cells

QUESTIONS