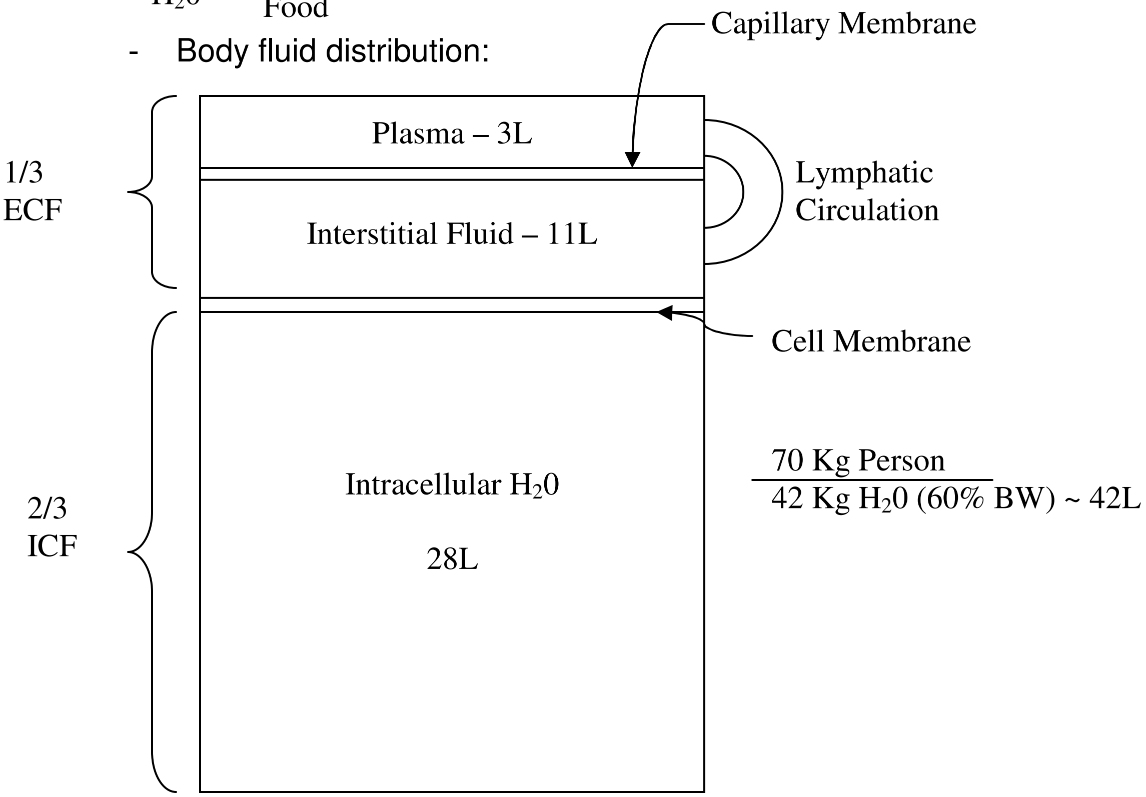
Body Fluid Dynamics

I. Body fluids

- Must remain constant
- Intake = output

Metabolic H_20 | Free H_20 | Preformed H_20 in Food | Urine | Feces | Sweat | Insensible H_20 loss

- Body fluid distribution:



- Edema = excess fluid in body tissues
  - Intracellular
  - Extracellular

<u>Causes</u>:

Increase in Capillary Filtration Coef.
- Histamine
- Bradykinin
- ↑ Capillary Perm.

Lymphatic system blockage

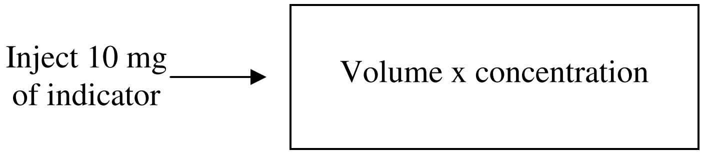
Δ in starling forces
- ↑ cap. pressure
- ↓ oncotic pressure

- Fluid composition
  a. Intracellular
    i. ↑ [K+]
    ii. ↑ [Protein]
    iii. ↓ [Na+], [Cl-], [Ca++]

  b. Extracellular

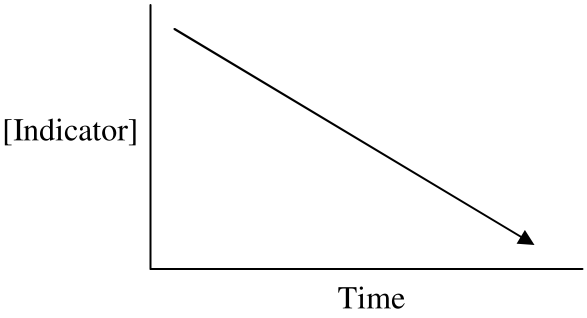
Plasma	Intersitial
↑ Protein	↓ Protein
↑ cations	

- Measuring fluid volumes
  - Indicator dilution principle →



Mass = Vol. x conc.
(indic)…therefore
10mg = vol. x (.01mg/L)

- assumptions:
  1. indicator has to spread throughout entire compartment
  2. indicator has to disperse only in compartment of interest
  3. Indicator is not metabolized or excreted



- Plasma Volume → use radio labeled albumin
- ECF → use substance that will not spread to cells (sucrose, radio labeled Na+ or Cl-
- Total body water → use tritium or deuterium oxide
- ICF → by subtraction

II. Kidneys

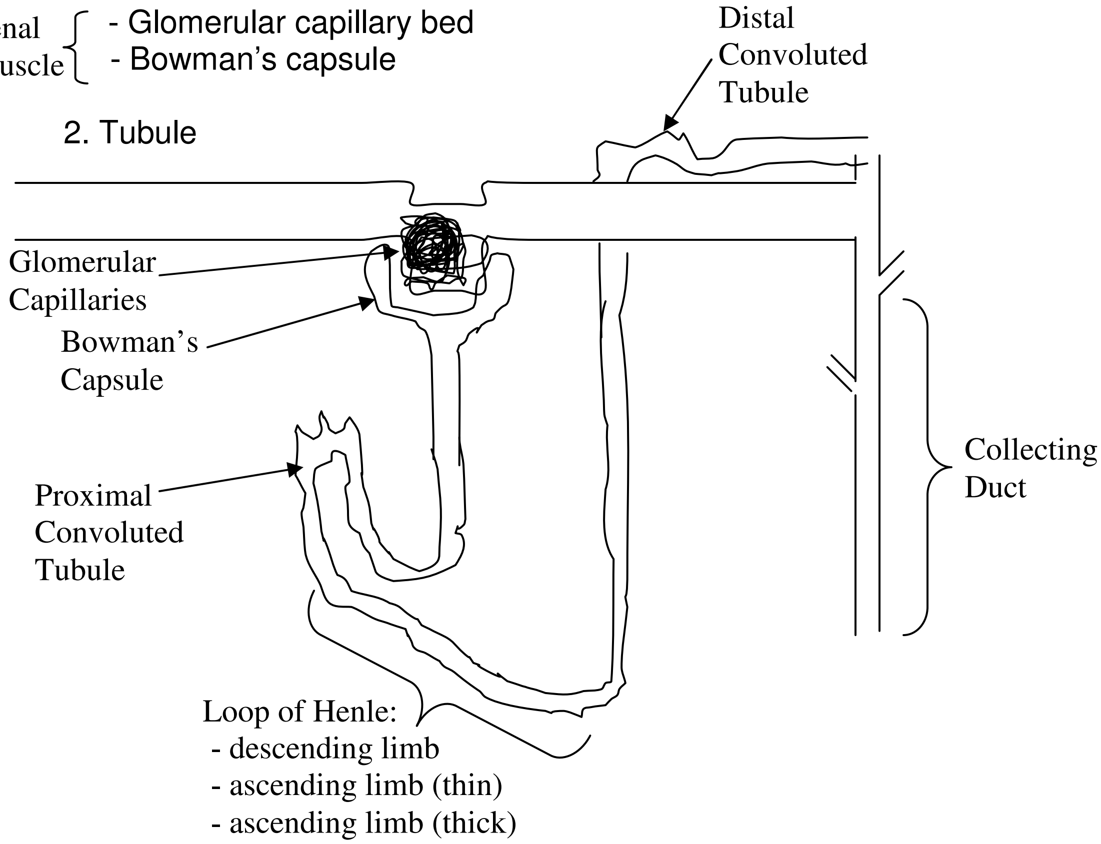
- Regulation of long term blood pressure
- Regulation of RBC production (EPO)
- Regulation of H20 electrolyte balance
- Regulation of osmolarity
- Regulation of acid/base balance
- Excretion of metabolic waste and foreign chemicals
- Glucose synthesis
- Ca++ and P regulation
- Vitamin D production

A. Nephron

- functional unit of the kidney (composed of glomerulus and tubule)
- ~ 1 million/kidney
- not regenerated
- 2 major components:
  1. Glomerulus

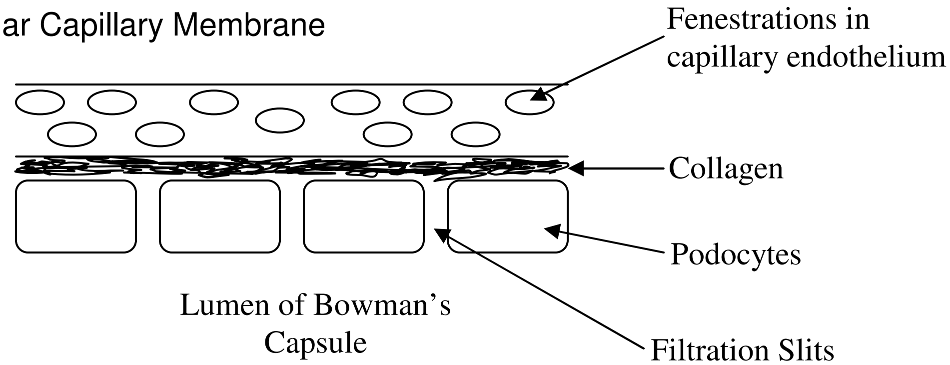
     Renal corpuscle
     - Glomerular capillary bed
     - Bowman's capsule

  2. Tubule



- Types of nephrons:
  1. Cortical = outer cortex; short loops of henle
  2. Juxtamedullary = long loops of henle
     - help to concentrate urine
     - vasa recta = special capillary bed running in same direction as loop of henle

B. Glomerular Capillary Membrane



III. Renal Physiology

- ~1200mL of blood can move past glomeruli each minute
  - ~650mL is plasma
  - ~125 mL of the plasma is forced into renal tubules (equivalent to filtering the entire plasma volume up to 60x/day).
  - b/c of this much activity, the kidney's use ~20-25% of all O_2 in the body.

- Filtrate formed is the precursor to urine
  - filtrate = everything in plasma (minus proteins)…by the time it reaches the collecting ducts almost all H20, nutrients, and ions have been removed.
  - after all molecules are removed, this is considered urine.

- Kidneys filter ~180L/day…of this amount, only 1% usually leaves the body as urine…the other 99% returns to the general circulation.

- There are <u>3</u> major processes leading to urine formation:
  - Glomerular filtration
  - Tubular reabsorption
  - Tubular secretion

<u>3 options here:</u>
- filtered; not reabsorbed
- filtered; reabsorbed
- filtered; secreted (K+)

A. Glomerular Filtration

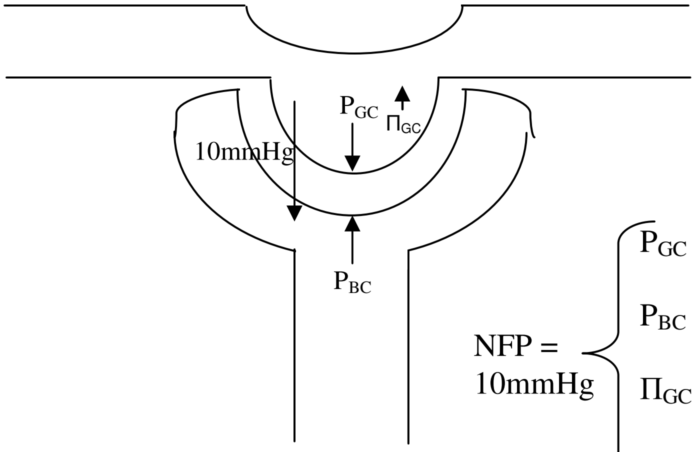
- Passive process in which hydrostatic pressure forces fluids and solutes through the membrane.
- Why is the glomerulus so efficient?
  - Membrane has ↑S.A. and is highly permeable to H20 and solutes.
  - Glomerular BP is much higher than in other capillary beds; results in ↑ <u>net filtration pressure.</u>
- Since plasma proteins are too large to move out of capillaries this maintains the colloid osmotic pressure (Π_{cap}) of glomerular blood.
- Maintaining the Π_{cap} prevents the loss of H20 into the renal tubules
  - P_{GC} = Blood pressure in glomerular capillaries ~ 55mmHg
  - Π_{GC} = Osmotic pressure in glomerular capillaries ~ 32mmHg
- If plasma proteins are in the urine, this is usually indicative of a malfunction in the filtration membrane.
- So what is Net Filtration Pressure (NFP)?
  - Pressure responsible for filtrate formation
  - Involves the glomerular hydrostatic pressure (HP_G or P_{GC})
    - Chief factor pushing H20/solutes out of blood and across the filtration membrane.
  - However, theoretically, the colloid osmotic pressure in Bowman's capsule (Π_{BC}) should pull the filtrate into the

    tubule…this pressure is essentially 0mmHg b/c no proteins enter the capsule.
  - HP_G is opposed by <u>2</u> factors:
    - Colloid osmotic pressure of glomerular blood (OP_G/Π_{GC})
    - Capsular hydrostatic pressure (HP_c or P_{BC})
  - Using the value for each, NFP can be calculated:
    - $NFP = P_{GC} – (\Pi_{GC} + P_{BC})$
    - NFP = 55 mmHg – (30 mmHg + 15 mmHg)
    - NFP = 10 mmHg!!!

- So how much filtrate is formed each minute?
  - This is the glomerular filtration rate, or GFR.
  - <u>3</u> factors influence GFR:
    - S.A. available for filtration
    - Membrane permeability *
    - NFP *

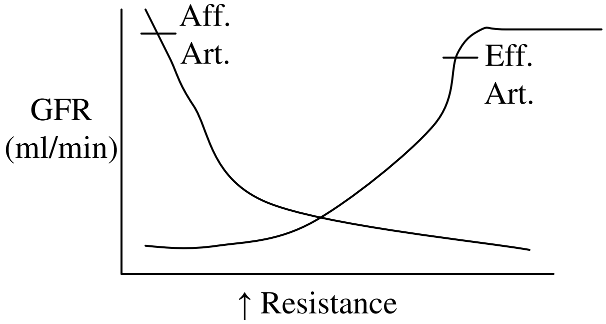
This can be represented by the formula:
- $GFR = K_f$ x NFP
- Where K_f is the capillary filtration coefficient, a measure of memb. Permeability.

  - So…
    - Long term regulation of GFR → ΔK_f or Δ in filtration pressure
    - ↑ B.P. → ↑ P_{GC} → ↑ GFR

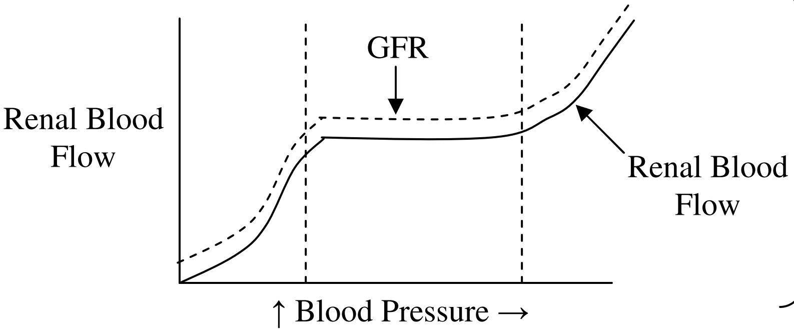


NFP = 10mmHg
- P_{GC} = 60mmHg
- P_{BC} = 18mmHg
- Π_{GC} = 32mmHg
- Π_{BC} = 0mmHg

- Δ's in resistance of arterioles also influences GFR:



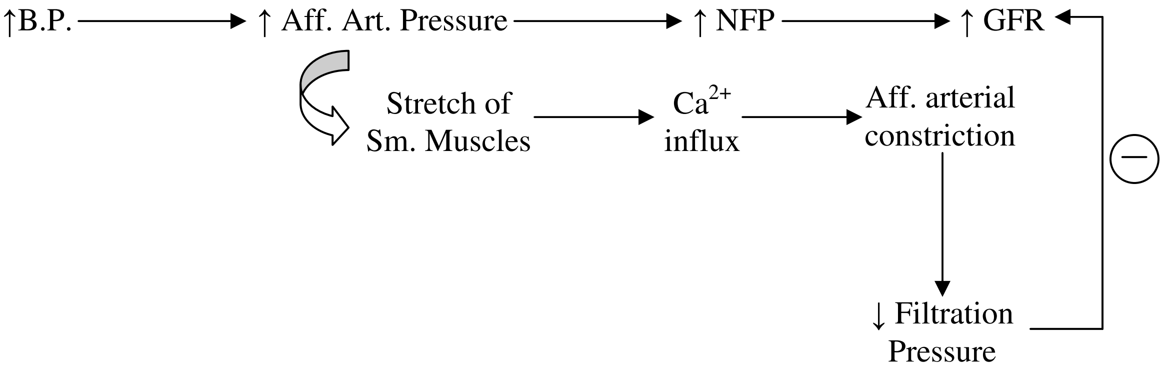
- another impt. Feature of GFR is that it can be maintained over a range of blood pressures:



- An ↑B.P. = ↑GFR

- However, autoregulation of this process helps maintain GFR levels

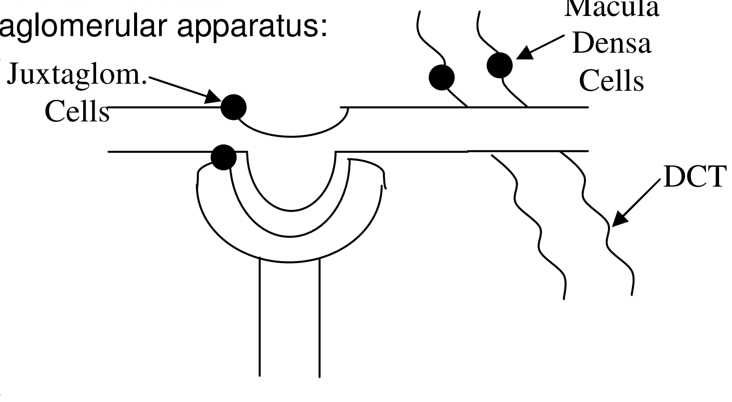
- There are 2 mechanisms to maintain GFR (intrinsic):
    - Myogenic

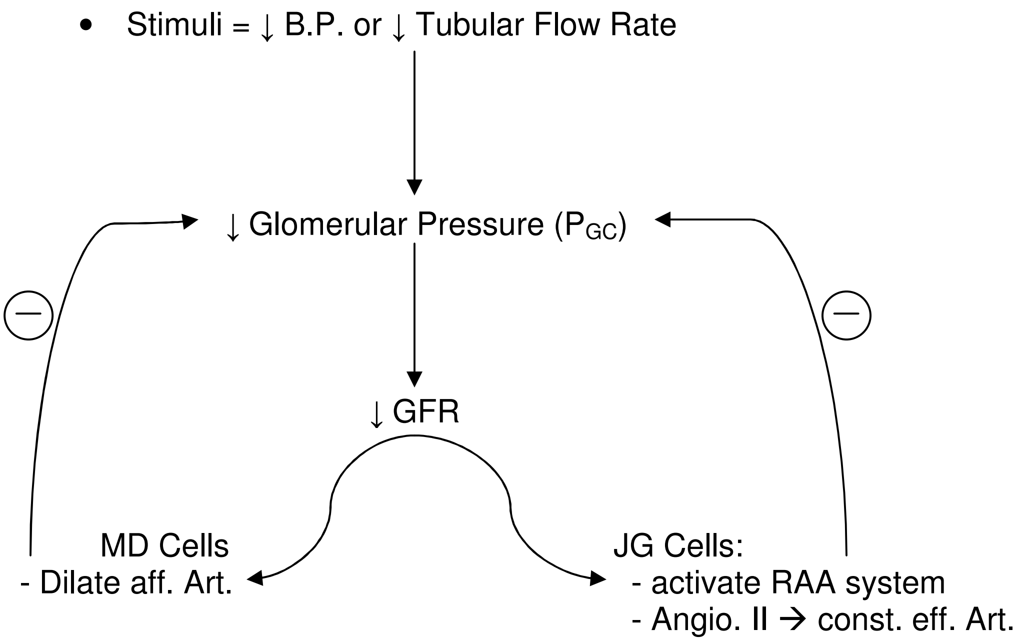


    - Tubuloglomerular Feedback
        - Juxtaglomerular apparatus:

2 Cell Populations:

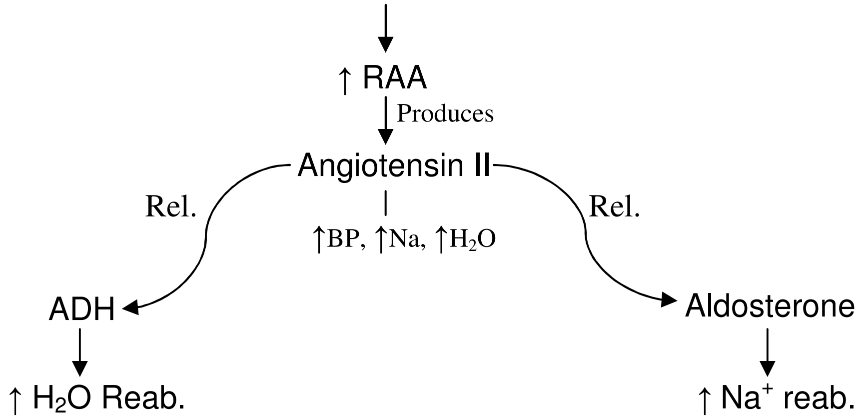
1. JG cells = Pressure
2. MD cells = [Na^+]; flow rate





- There are also <u>2</u> extrinsic controls:
  - SANS (stress response)
    - Major effect = constrict arterioles
    - Causes an ↑ in reabsorption and ↓ filtration
    - Epi/NE bind to α-AR in sm. muscle
  - Hormonal Control
    - RAA system (Angiotensin II)
      - Overall = ↑ Na^+ and H_2O reabsorption
        - Stimulates aldosterone prod/rel.
        - Constricts eff. Art.
        - Directly ↑ Na^+ reab. in proximal tubule by activating Na-K pump
        - Stimulates release of ADH
    - Aldosterone
      - Steroid hormone rel. from adrenal cortex
      - Acts on principle cells in dist. tubule/cort. collecting duct.
      - ↑ Na^+ reabsorption and ↑ K^+ secretion
        - Stimulates Na^+-K^+-ATPase on basolateral membrane
        - ↑ Na^+ channels or carrier proteins on luminal membrane
    - ADH
      - Peptide hormone rel. from posterior pituitary
      - ↑ H_2O permeability in distil tubule
        - Insert aquaporins in luminal memb.

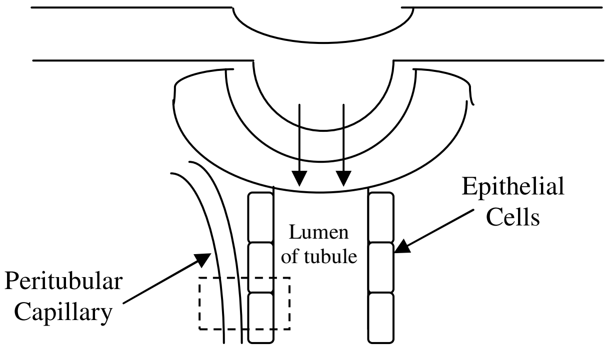
- Stimuli = ↓ B.P. or ↓ [Na^+]

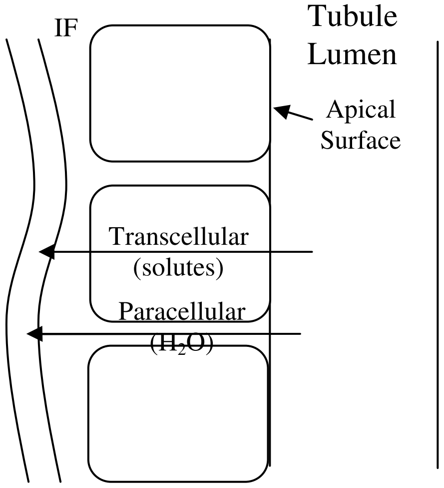


- ANP
  - Stimuli = ↑ heart stretch ⊖
  - Effects = ↓ Renin release
    ↓ Aldosterone release
    Dilate aff. art. → ↑GFR → ↑ Urine output

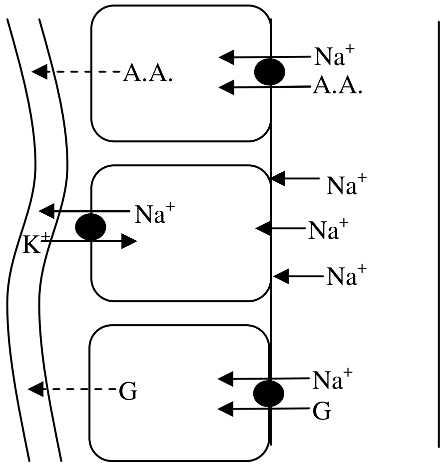
B. Tubular Reabsorption/Secretion

- Both act to alter the concentration of the filtrate
- ~180L/day filtered → 178L/day reabsorbed
- Tubular reabsorption is the movement of filtered solutes and H_20 from the tubule lumen into the plasma.





- Mechanisms:
    - Diffusion down gradients
        - e.g. H_20 by osmosis
    - Active transport
        - Primary
            - e.g. Na^+
                - Basolateral side
                    - Na-K pump
                - Luminal side
                    - Facilitated diffusion
        - Secondary
            - e.g. Glucose/Amino Acids
                - Na-K pump provides stored energy
                - Glu-Na cotransport/symport on luminal side
                - Glu moves down [ ] gradient into blood

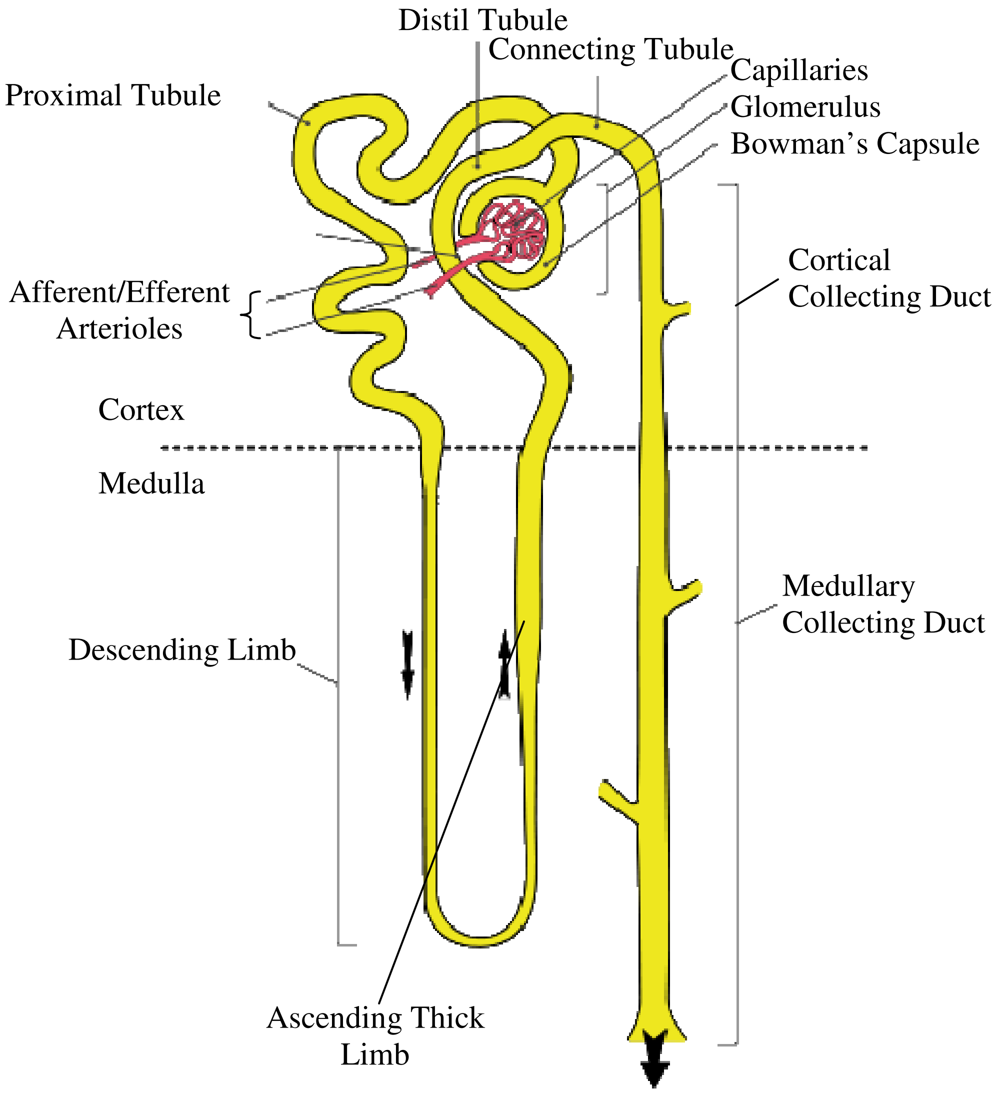


- Transport (tubular) maximum = the maximum amt. of a subst. that can be transported across the tubule membrane per unit time.
- Sometimes there is excess glucose that cannot be reabsorbed due to renal threshold.
- Renal Threshold = tubular load (mg/min) that exceeds the transport max.
- Other examples include: PO_4^{3-} and SO_4^{2-}

C. Nephron Anatomy

- Proximal Tubule
  - Largest reabsorbing segment (65-70% of filtrate)
  - Most secretion occurs here
  - Characteristics:
    - Brush border on luminal membrane
      - ↑ S.A. for reab.
      - ↑ density of carrier proteins
      - ↑ mitochondria
      - ↑ Na-K ATPase
      - Leaky epithelial. Junctions
        - Na^+, H_20, Glu, Vitamins
- Descending Thin Limb
  - Few mitochondria
  - No brush border
  - ↓ Active Transport
  - Permeable to H_20 + urea
- Ascending Thick Limb → diluting segment
  - Impermeable to H_20 + urea
  - ↑ Active Transport
    - Na-K-2Cl cotransporter (reabsorption)
    - Na-H counter transport (Na reabs; H secreted)
    - Reabsorption of Ca^{2+} and Mg^{2+}
- Distal Tubule → site for regulation
  - Early DT = diluting
    - Impermeable to H_20 + urea
    - Site of JG apparatus (macula densa cells)
    - ↓ Active Transport
  - Late DT/Connecting Tubule/Cortical Collecting Duct
    - Impermeable to urea
    - Permeability to H_20 varies
      - w/o ADH → impermeable
      - w/ADH → permeable
    - Principle Cells
      - Na^+ reabsorption
      - K^+ secretion

        } Both are acted on by aldosterone
    - Intercalated Cells
      - K^+, HCO_3 reabsorption
      - H^+ secretion
- Medullary Collecting Duct
  - Last segment to act on filtrate
  - Permeable to H_20, controlled by ADH
  - Permeable to urea (allows for reabsorption)
  - H^+ secretion



D. Regulation of Reabsorption
- Local Factors:
  - Glomerulotubular balance
    - ↑ GFR → ↑ reabsorption
  - Peritubular Starling Forces
    - e.g. Angiotensin II → ↑ Reabsorption
      - via constricting eff. Arterioles → ↓ pressure in peritubular capillaries.
- Nervous Control
  - See page 7
- Hormones (humoral factors)
  - See page 7

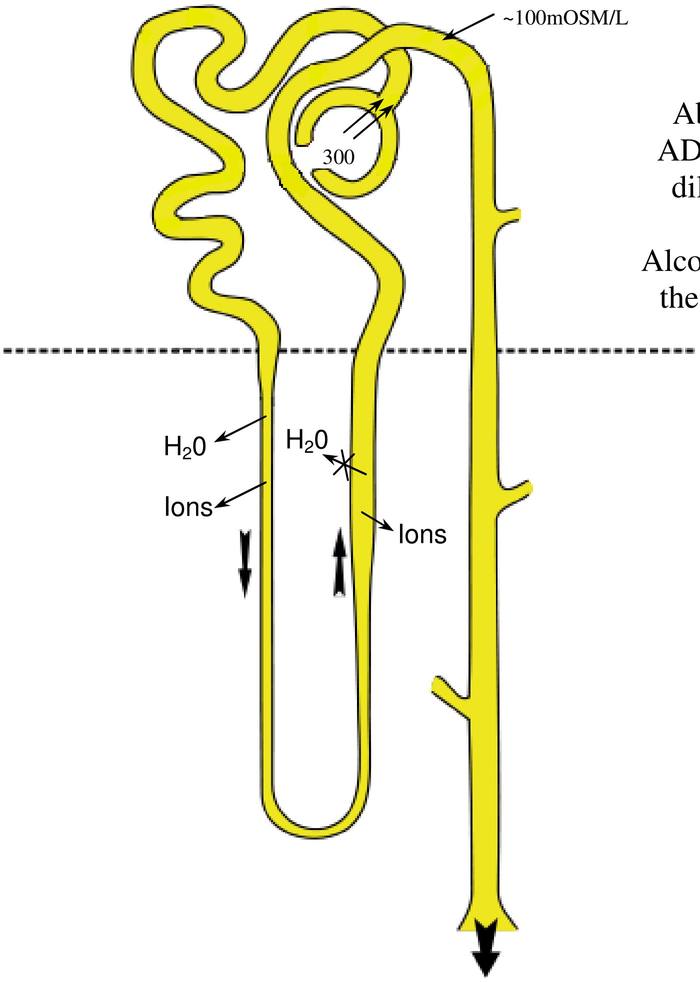
E. Clearance

- Volume of plasma that is cleared of a substance by the kidneys per unit time.
- Units = ml/min
  - $C_x = \frac{U_x (V_x)}{Px}$; where: x = substance tested
    C = Clearance
    U = Urine concentration (mg/ml)
    V = Urine flow rate (ml/min)
    P = Plasma Concentration (mg/ml)

- Any substance used to measure Clearance also measures GFR…the substance can be filtered, but not reabsorbed or secreted (Inulin/Creatinine).
  - If reabsorption occurs:
    - Clearance < GFR
  - If secreted into tubule:
    - Clearance > GFR

IV. Dilution of Urine

- Due to absence of ADH; loss of excess H_20 through excretion in urine
- $Plasma_{osm}$ = 300 mOSM/L
- $Filtrate_{osm}$ = 300 mOSM/L



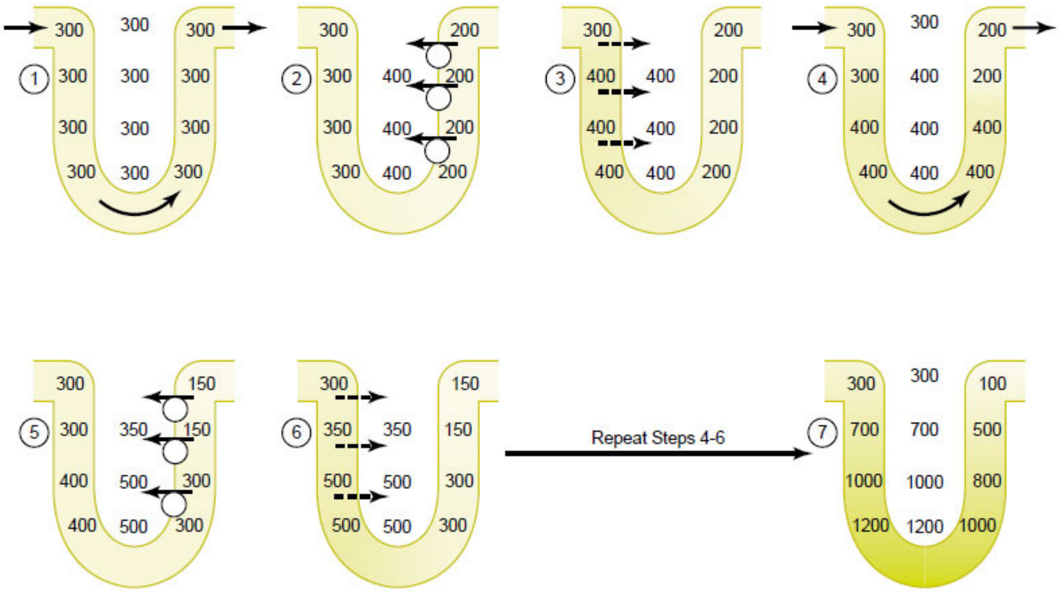
Absence of ADH leads to dilute urine

Alcohol inhibits the release of ADH

V. Concentration of Urine
- Max_{OSM} of urine in humans ~ 1200 mOSM/L
- Sea water ~ 2400 mOSM/L
    - 1L = 2400 mOSM of electrolytes
    - 2L of urine

A. Requirements
- ADH
    - To reabsorb H_20
- High osmolarity in renal medullary interstitial fluid

Produced by countercurrent multiplier
- CC flow in loop of Henle
- Active Transport (Na-K-2Cl)
- Diffusion of H_20; permeability



Countercurrent multiplier system in the loop of Henle for producing a hyperosmotic renal medulla. (Numerical values are in milliosmoles per liter.)

- Urea contributes ~500 mOSM/L to the Renal I.F. osmolarity

B. Maintaining the Osmotic Gradient
- Vasa Recta → acts as the countercurrent exchanger (maintains, not creates)
- At bottom of loop, $Plasma_{osm}$ = 1200 mOSM/L
- At top of ascending loop, $Plasma_{osm}$ = 310 mOSM/L
    - Vasodilators ↓ [urine]
- Other factors affecting the gradient:
    - Length of the loop of Henle

        - Longer = greater concentration of urine
    - % of nephrons that juxtamedullary (long loops)
        - More = ↑ urine concentration
    - Diet → ↑ Protein → ↑ osmolarity of urine

VI. Diuretics

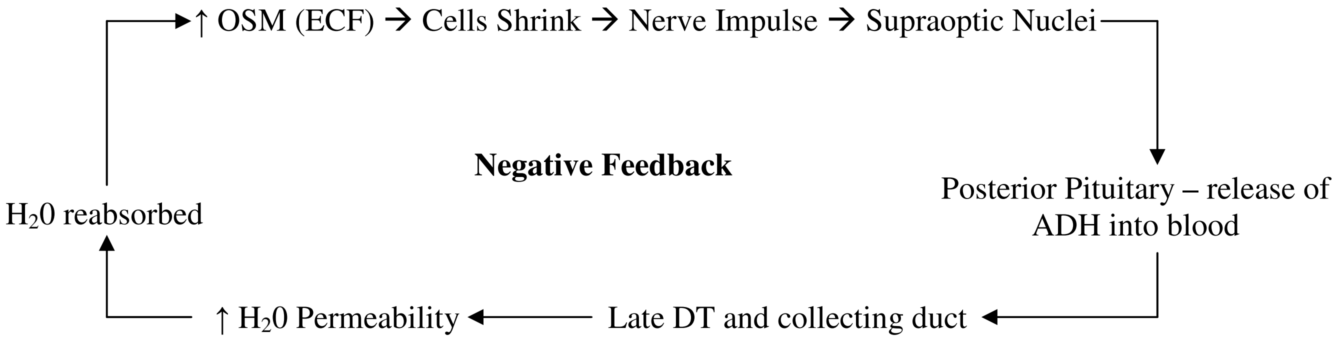
- Substance that increases urine volume output
- Clinically used to ↓ edema and hypertension
    - Cheaper than Ca^{2+} channel blockers or ACE inhibitors
- Types:

Clinical

- Osmotic diuretics
    - Agents that are filtered, but not readily reabsorbed
        - e.g. manitol, sucrose, urea, *glucose – diabetes
- Loop diuretics
    - Work in ascending thick limb of loop of Henle
    - Block Na-K-2Cl cotransporter
        - e.g. Lasix® (furosemide)
- Thiazides
    - Inhibits Na-Cl reabsorption in early DT
- Competitive inhibitors of Aldosterone
    - e.g. Spironolactone (aldactone)
    - act on principle cells to prevent reabsorption
- Na- channel blockers
    - Collecting ducts
    - Prevents Na$^+$ from being reabsorbed
- Carbonic Anhydrase Inhibitors
    - Prevents reabsorption of Na$^+$ and HCO$_3$
    - Acidosis can occur
- Alcohol
    - ADH antagonist
- Xanthenes
    - Caffeine
    - Theophylline

VII. Control of Osmolarity of ECF

- ~300 mOSM/L; 142 mOSM/L comes from Na$^+$
- Osmoreceptor-ADH System:
    - Main stimulus = Δ in osmolarity
    - Receptor cells = Osmoreceptors; Neurons in hypothalamus



  - Other stimuli for ADH release:
    - ↓Blood Pressure (from baroreceptors)
    - ↓Cardiac stretch (via low pressure receptors)
- Thirst System:
  - Stimulus = Δ in osmolarity of ECF
  - Receptors = Osmoreceptors
    - ↓OSM_{ECF} → Osmoreceptors will stimulate thirst; occurs via the preoptic thirst center in the hypothalamus
  - Secondary Stimuli
    - ↓Blood pressure; ↓ECF volume
    - Angiotensin II
    - Dryness of mucus membranes