ANATOMY and PHYSIOLOGY

Renal Vasculature: Vessels are listed in order of blood flow.

- **Renal Artery**
- **Interlobar Arteries:** Descend between kidney lobules to the corticomedullary junction.
- **Arcuate Arteries:** They divide the kidney cortex from the medulla.
- **Interlobular Arteries**: Branch from the corticomedullary junction back outward toward the capsule.
- **AFFERENT ARTERIOLES**: Primary arterioles that provide incoming blood to the glomerulus.
    - A major source of pressure drop in the kidney system.
- **GLOMERULAR CAPILLARIES:** Filter blood into the glomerulus, and then unfiltered blood continues to efferent arterioles.
    - **Net Filtration:** *Hydrostatic Pressure > Oncotic Pressure*
- **EFFERENT ARTERIOLES:** Primary arterioles that contain the remaining blood that was not filtered by the glomerulus.
    - A major source of pressure drop in the kidney system.
- **VASA RECTA:** The continuation of efferent arterioles, *in the medulla*
    - FNXN: Counter-Current Exchange. They run parallel to the collecting tubules in juxtamedullary nephrons.
- **PERITUBULAR CAPILLARIES:** The continuation of efferent arterioles, *in the cortex*.
    - **Net Reabsorption:** *Oncotic Pressure > Hydrostatic Pressure*.
        - They have a **high oncotic pressure** because of the high concentration of blood proteins that didn't filter.
- **Interlobular Veins**
- **Arcuate Veins**
- **Interlobar Veins**
- **Renal Vein**

GLOMERULUS: Initial filtration of blood.

- STRUCTURE: Layers of the glomerular filter, from blood-space to bowman's space.
    - **ENDOTHELIAL CELLS:** Capillary endothelial cells are *fenestrated.*
    - **PODOCYTES:** Glomerular epithelial cells.
        - They extend interdigitating **Foot Processes** onto the capillary wall, which can separate from each other when mesangial cells contract.
        - Tight Junctions between foot processes serve as an additional barrier to filtration (in addition to the GBM).
    - **FILTRATION SLITS:** The spaces between the foot processes, through which blood and blood solutes pass.
        - The width of the slits can vary from 240 angstroms to 3000-5000 angstroms, under the influence of the mesangial cells.
        - **MESANGIAL CELLS:** They are interstitial cells in the glomerulus.
            - FNXN: They can phagocytose debris from the interstitium.
    - **GLOMERULAR BASEMENT MEMBRANE** (GBM): *The GBM is the primary barrier to filtration.*
        - Layers:
            - **Lamina Rara Externa**: Facing the capillary space.
            - **Lamina Densa**: Thick middle part.
            - **Lamina Rara Interna**: Facing the tubular space.
        - **NEGATIVE CHARGE:** *The basement membrane has an overall negative charge due to presence of **Sialic Acid** in the Glomerular membrane.*
            - This negative charge makes the glomerulus repel large negative proteins in the blood so they don't filter.

    - **BOWMAN'S SPACE:** Contains the glomerular filtrate.
- GLOMERULAR FILTRATE: *It is identical in composition to blood except it doesn't contain large anionic blood proteins (such as Albumin and other protein-transporters).*
    - Negative charges don't get through:
        - **Dextran:** Neutral dextran has a fractional clearance of 0.19, while **Dextran Sulfate** (negatively charged) has 1/10th that value: 0.015.
        - **Albumin:** Not a chance, under normal circumstances.
- Pathologies:
    - **GLOMERULONEPHRITIS:** Immune reactions in kidneys ------> proteolytic enzymes destroy the glomerular barrier, such that large blood proteins *can* get through.
        - *Experimental evidence says that Glomerulonephritis causes the Glomerular BM to **lose its negative charge**,* so that the additional barrier against anionic proteins disappears.

GLOMERULAR FILTRATION PRESSURE: $P_f = (P_{gc} - P_t - PI_b)$

- Variables:
    - P_f = Glomerular Filtration Pressure
    - P_{gc} = **Glomerular Capillary Hydrostatic Pressure.**
        - The hydrostatic pressure in renal capillaries is higher than in capillaries in other systems, because of the higher resistance of the efferent arterioles.
    - P_t = Tubular Hydrostatic Pressure
    - PI_b = Glomerular Oncotic Pressure
- ***As glomerular blood is filtered, the remaining blood increases in oncotic pressure (PI_b), which allows for reabsorption in the peritubular capillaries*.**

GLOMERULAR FILTRATION RATE (GFR): The rate, in mL/min, at which blood is filtered through the glomerulus: **$GFR = K_f (P_{gc} - P_t - PI_b) = (K_f)x(P_f)$**

- **K_f = FILTRATION COEFFICIENT:** A constant representing the permeability of the glomerular filter.
    - You can calculate a value for K_f by measuring GFR and P_f.
- REGULATION OF GFR and RBF: In general, GFR changes in the same direction as RBF, RBF usually changes more profoundly.
    - *Lower K_f (less permeability) ------> lower GFR*
        - This is somewhat compensated by a *slower rate of rise of oncotic pressure* which is a direct consequence of the lower GFR. That leads to a slightly higher P_f, which balances off the GFR a little.
    - ARTERIOLAR CHANGES:
        - ***Efferent Arteriolar Vasoconstriction ------>***
            - LOWER RBF
            - HIGHER GFR, because of higher P_{gc}
        - ***Afferent Arteriolar Vasoconstriction ------>***
            - LOWER RBF
            - LOWER GFR, because of lower RBF
        - ***Afferent Arteriolar Vasodilation ------>***
            - HIGHER RBF
            - HIGHER GFR, because of higher RBF
        - COMBINED CHANGES: When two or more factors both change, RBF is generally affected more than GFR. GFR remains relatively stable.
    - FACTORS AFFECTING ARTERIOLES:
        - Resting tone in the arterioles, maintained by intrinsic myogenic activity.
        - **SYMPATHETICS** innervate both afferent and efferent arterioles to cause vasoconstriction.

        - Epinephrine and Norepinephrine *both cause **vasoconstriction** in the kidneys*, because alpha-Receptors greatly outnumber beta-Receptors.
            - Moderate sympathetic increase ------> decrease RBF with little change in GFR.
            - Large increase in sympathetics ------> stop glomerular filtration entirely.
        - ATRIAL STRETCH RECEPTORS have a more significant effect on the kidneys than the baroreceptors. This suggests that the kidneys respond to *blood volume* changes more than to blood pressure changes.
    - **RENIN / ANGIOTENSIN II** leads to vasoconstriction.
        - Drugs:
            - **Saralasin** blocks the effects of Angiotensin II
            - **Captopril** blocks ACE, thus preventing conversion to Angiotensin II
        - Biosynthetic Pathway: JGA Cells secrete Renin in response to low tubular osmolarity.
            - Renin converts **Angiotensinogen ------> Angiotensin I** in the kidney.
            - **ACE** converts **Angiotensin I ------> Angiotensin II** in the lungs.
            - **ANGIOTENSIN II:** It causes water retention (reabsorption) by two mechanisms:
                - Direct action on tubules to promote Na^+ and water reabsorption
                - Indirect action on kidneys by stimulating **Aldosterone** secretion in adrenal cortex.
    - **PROSTAGLANDIN E_2 (PGE_2):** *Vasodilator*. Its release is stimulated by Angiotensin II, and it acts primarily on the *afferent arteriole.* It counteracts the actions of Angiotensin II.
        - Because Angiotensin II is a vasoconstrictor, this vasodilatory effect *modulates the vasoconstrictor effects of the Angiotensin II*.
        - Because of the counteracting effects of **Angiotensin II + PGE_2**, the net is to **reduce RBF** while keeping GFR relatively constant.
    - **ENDOTHELIN** is released locally and causes vasoconstriction of primarily the efferent arteriole ------> reduce RBF
- **RENAL AUTOREGULATION:** The intrinsic response of the kidney to changes in blood pressure, independent of innervation.
    - *Smooth Muscle Myogenic Response:* The smooth muscle response to pressure accounts for some of this autoregulation.
    - **TUBULO-GLOMERULAR FEEDBACK:** *Macula Densa* senses changes in the **tubular fluid flow rate** and modifies the arterioles accordingly.
        - A higher arterial blood pressure will lead to higher tubular fluid flow: MABP ------> Capillary Pressure ------> Tubular Flow ------> Macula Densa senses the higher tubular flow ------> Resistance in Afferent Arteriole ------>Blood pressure
        - This feedback is on a per-nephron basis. Macula Densa cells will affect the resistance *only in the afferent arteriole of that local nephron*.
        - Macula Densa may sense Na^+ or Cl^- concentration. We don't know for sure what it senses
- **JUXTAGLOMERULAR APPARATUS:** The juxtaposition of the DCT (macula densa cells), squeezed in between the efferent and afferent arterioles (JGA cells).
    - FNXN: The JGA ultimately regulates Glomerular Filtration Rate by regulating the vascular tone of the Afferent and Efferent Arterioles, via **Tubulo-glomerular Feedback**.
    - JGA CELL TYPES / HISTOLOGY:
        - **MACULA DENSA:** Forms the *tubular part* of the Juxtaglomerular Apparatus.
            - The Macula Densa cells form part of the wall of the DCT.

        - FNXN: They sense Na^+ concentration and tubular fluid flow in the tubular filtrate, and feedback to the Juxtaglomerular Cells accordingly.
    - **GRANULAR (JGA) CELLS:** Form the *vascular* part of the Juxtaglomerular Apparatus, in the walls of the afferent and efferent arterioles.
        - *They receive input from the Macula Densa cells.*
    - **EXTRAGLOMERULAR MESANGIAL CELLS:** Interstitial cells in the JGA.
        - *They receive input from the Macula Densa cells.*
        - When they contract, they *reduce glomerular capillary surface area* available for filtration, which ultimately can lead to lower glomerular filtration rate.
  - SUMMARY: The JGA is under both intrinsic and extrinsic control.
    - NEURAL (Extrinsic Sympathetic)
    - HUMORAL (Renin, Angiotensin, PGE_2)
    - ARTERIAL PRESSURE (Autoregulation)
    - TUBULAR FLUID (Tubulo-glomerular Feedback)
- GFR and DIURESIS: GFR has more pronounced effects on salt and water reabsorption when the GFR is *high* then when it is low.

TRANSPORT SYSTEMS:

- **Capacity-Limited Systems:** As in Glucose Transport, they are limited by saturation of available receptors. While there may be a gradient driving the transport, the gradient does not normally present a barrier to transport.
- **Gradient-Limited Diffusion:** Secondary active transport of ions through intracellular and paracellular pathways.
  - **Back-diffusion** of ions will occur simultaneously with the transport.
  - The *net transport* is the difference between the active transport and the back diffusion. As long as enough ATP is available, transport will move in the positive direction.
- Primary Active Transport
- Secondary Active Transport

PROXIMAL CONVOLUTED TUBULE (PARS CONVOLUTA):

- STRUCTURE
  - **Apical Microvilli** and **Basolateral Folds** drastically increase surface area.
  - **Tight Junctions** regulate movement
  - **Paracellular Spaces** exist between cells. Some movement of fluid and ions occurs through these spaces.
- PERMEABILITY:
  - High permeability to water, due to presence of **Aquaporin** channels.
  - High permeability to ions = *high conductance.* Lots of ions will move through the *paracellular path* in the proximal tubule.
  - Thus, it has a *low electrochemical gradient* needed to drive the transport.
  - SUMMARY: **High Rate, Low Gradient** Transport. Lots of fluid and electrolytes are reabsorbed virtually isotonically -- *the concentration of the filtrate doesn't change* under normal circumstances.
- ORGANIC REABSORPTION: 60-70% of Na^+, Cl^-, HCO_3^-, and K^+ occurs in proximal tubules. 100% of glucose reabsorption should occur as well.
  - UREA: Proximal tubule is permeable to urea, but urea concentration still increases in this part because more water is reabsorbed than urea.
  - URIC ACID REABSORPTION. It is both secreted and reabsorbed, but net reabsorption usually occurs. *The Proximal Tubule is the only place where uric acid transport occurs*.
  - GLUCOSE: Na^+-Glucose Cotransport. It is a capacity-limited system, i.e. you will run out of transporters before the gradient is eliminated.
    - Complete reabsorption occurs at concentrations lower than 250 mg / dL

        - All transporters are filled at concentrations above 350 mg / dL
        - **D-Galactose** and **D-Fructose** compete for the same transporters.
    - AMINO ACIDS: Na^+-Cotransport. Almost complete reabsorption occurs at the proximal tubules. The kidneys do not regulate blood levels of amino acids.
    - PROTEINS: Small protein-hormones (like ADH, PTH, Insulin) are reabsorbed by pinocytosis and then broken down inside the cells, and then transported back into the blood.
- ORGANIC SECRETION
    - ORGANIC ANION SECRETION: The proximal tubule actively and non-specifically secretes lots of organic anions that are bound to plasma carrier-proteins.
        - These anions weren't originally filtered because they were bound to plasma proteins. The secretion allows for the unloading of these proteins into the filtrate.
        - **Prostaglandins** are secreted in the proximal segment so that they can be delivered to the distal tubule where they act.
    - ORGANIC CATION SECRETION: **Creatinine** (to some extent) and other organic cations are secreted.
    - URIC ACID SECRETION occurs at high levels when blood levels of uric acid are high. The amount of secretion is dependent on plasma concentration of urate.
    - DRUGS: Lots of drugs are secreted in the proximal tubule.
        - **Furosemide** and **Bumetanide** are two diuretics that are secreted in the proximal tubule, so that they can be delivered to more distal tubules where they act.
- SALT REABSORPTION / ION CHANNELS: Salt reabsorption in the proximal tubule does not appreciably affect the composition of blood plasma, but it can have a **major effect on the volume** of plasma.
    - **Na/K-ATPase**: The primary engine to create the gradient. The pump operates way below a saturated level at a steady state, so more Na^+ coming into the cell will increase the rate of pumping, thus maintaining the gradient.
    - **Na^+-REABSORPTION:**
        - **Na^+-CHANNELS:** Straight Na^+ transport through apical channels. This is a minor contributor to total Na^+ transport.
        - **Na^+/H^+-ANTIPORT:** Bring Na^+ in and kick H^+ out into the filtrate. This is a *major contributor to Na^+ reabsorption*.
            - *This mode of Na^+ transport predominates in the first third of the proximal tubule*.
            - The pH inside the cell is maintained by HCO_3^-/CO_2 homeostasis. ***The loss of the H^+ inside the cell results in creation of another H^+ and HCO_3^-***
            - **Angiotensin II** stimulates Na/H exchange and thus promotes Na^+ reabsorption.
        - **Na^+/GLUCOSE-SYMPORT:** The channel is driven by Na^+ gradient, and some Na^+ is reabsorbed by this path, dependent on how much glucose there is.
    - **HCO_3^--REABSORPTION:** Complicated, but net reabsorption of HCO_3^- occurs.
        - IN FILTRATE: From Na/H Antiport, the secreted H^+ reacts with HCO_3^- in the filtrate, to form CO_2 and H_2O.
        - INSIDE CELL: More HCO_3^- is being created by the net transport of H^+ outward. *This HCO_3^- is transported back into the blood via **HCO_3^-/Na^+ symport** in a 3:1 ratio*.
        - **Carbonic Anhydrase** is present on both brush-border and inside cell. It speeds the process of HCO_3^- reabsorption in both cases.
        - As HCO_3^- reabsorption increases, Cl^- concentrations in the filtrate become relatively higher, driving their paracellular transport in the later sections of the tubule.
    - **Cl^--REABSORPTION:**
        - **Cl^--BASE ANTIPORT:** Cl^- is reabsorbed into the cell, and base is kicked out into lumen. This transporter works in conjunction with the Na^+/H^+-Antiport.
            - The base can be oxalate, OH^+, HCO_3^-, or formate.

        - The net result of these two channels is transport of NaCl into the cell! *This mode of Na^+ transport predominates in the latter two thirds of the proximal tubule*.
    - **PARACELLULAR** reabsorption of Cl^- occurs in later segments. This transport is driven by a *rise in Cl^- concentration in the early segments of the tubule*. Cl^- concentration rises early on because reabsorption of other ions (Na^+ and HCO_3^-) is occurring more readily.
    - **K^+-Cl^--Symport** on basolateral membrane allows Cl^- to get back into bloodstream.
  - **WATER REABSORPTION** is driven by all of the above ion-transporters.
    - The gradient for water reabsorption is small, but the rate is high!
    - Water flows back through PARACELLULAR spaces ------> ISF ------> **Peritubular Capillaries** which have low hydrostatic pressure and high oncotic pressure.
- PROXIMAL TUBULE REABSORPTION: Na^+ and water are always reabsorbed isosmotically. Thus anything that affects the reabsorption of one thing will also affect the reabsorption of the other.
- **PRIMARY INHIBITION of WATER REABSORPTION:** The presence of poorly absorbed solute decreases water reabsorption in the proximal tubule. *The higher the concentration of impermeable solute in the filtrate, the sooner water reabsorption will stop, the less water will be reabsorbed*.
    - As you proceed through the proximal segment, the concentration of impermeable solute in the filtrate will relatively increase.
    - That increase in osmolarity must be offset by a decrease in the osmolarity of something else.
    - UREA: Urea concentration in proximal segment relatively increases as you go forward ------> water reabsorption is inhibited.
        - **High Protein Diet** ------> high UREA in filtrate ------> slight **solute diuresis**.
    - **MANNITOL** is an osmotic diuretic for similar reasons. It is poorly reabsorbed by the Nephron.
    - **ACETAZOLAMIDE** is a diuretic that works by blocking transport in the proximal tubule.
  - **Angiotensin II** stimulates the Na^+/H^+ antiport in the proximal tubule.
    - MECH: $G_{INHIBITORY}$ ------> *decrease levels of cAMP* ------> *disinhibition* of channels. *cAMP normally inhibits this channel*.

PROXIMAL STRAIGHT TUBULE (PARS RECTA):

LOOP OF HENLE:

- **THIN DESCENDING LIMB of LOOP of HENLE:**
  - TRANSPORT: No active transport occurs in the descending limb.
    - *In the Medulla*, reabsorption of water will continue to occur into the interstitium.
    - *In the Medulla*, some NaCl and urea will move from the interstitium back into the tubular fluid.
  - PERMEABILITY: Epithelium is permeable to water and small ions.
- **THIN ASCENDING LIMB of LOOP of HENLE:**
  - PERMEABILITY: *Low permeability* to water starting in the thin ascending limb.
- **THICK ASCENDING LIMB of LOOP of HENLE:** *The major contributor to the counter-current multiplier. It generates a **hypotonic filtrate** which it delivers to the distal tubule*.
  - PERMEABILITY: *Very low permeability to water.*
  - TRANSPORT: **Moderate Rate, Moderate Gradient**.
  - FILTRATE CHANGES:

        - BEGINNING of TALH: The tubular fluid has high concentration of NaCl. NaCl is massively reabsorbed through the TALH.
        - END of TALH: *The filtrate is now hypoosmotic*.
    - **Na / K / 2Cl SYMPORT:** Electrically neutral secondary active transport of four ions at a time.
        - Some back-diffusion of K^+ occurs through apical K^+ channels.
        - **LOOP DIURETICS: FUROSEMIDE, BUMETANIDE**, inhibit this transporter. They are very potent diuretics.

DISTAL CONVOLUTED TUBULE (DCT): The distal tubule, in the kidney cortex.

- PERMEABILITY:
    - Permeability to water is variable, dependent on **ADH**:
        - *ADH Present ------> open Aquaporin pores ------> High permeability ------> water reabsorption ------> filtrate starts to become more hypertonic*
        - *ADH Absent ------> low permeability ------> no water reabsorption ------> filtrate remains hypotonic*
    - Permeability to electrolytes is very low = *low conductance*
    - Thus a very *high electrochemical gradient* is required to drive ion transport.
- TRANSPORT: **Low Conductance, High Gradient.** It uses *a lot of energy* (Na/K-ATPase) to drive even more Na^+ out of the tubular fluid.
    - It has more Na/K-ATPase transporters than the proximal tubule, because it requires more energy to maintain a strong enough gradient to keep driving Na^+ out at this point.
    - **Na/Cl SYMPORT** exists on apical membrane for further reabsorption of Na and Cl.
        - **THIAZIDE** is the diuretic that inhibits this port.
    - **PRINCIPLE CELLS** are found in the DCT, where they are sensitive to both Aldosterone and ADH (see Collecting Tubules below).
- SUMMARY: **Low Rate, High Gradient**. It can be made to vary the ratios

COLLECTING TUBULES:

- PERMEABILITY / WATER REABSORPTION
    - Permeability to water is variable, dependent on **ADH**.
        - *ADH Present ------> open Aquaporin pores ------> High permeability ------> water reabsorption ------> filtrate becomes very hypertonic ------> concentrated urine*
        - *ADH Absent ------> low permeability ------> water excretion ------> filtrate remains hypotonic ------> dilute urine*
    - Permeability to electrolytes is very low = *low conductance*. Thus a very *high electrochemical gradient* is required to drive ion transport.
- TRANSPORT: **Low Conductance, High Gradient**, with gradient maintained by massive Na/K-ATPases.
    - **PRINCIPLE CELLS:** Principle cells are found in both the cortical and inner medullary segments.
        - **APICAL Na+ CHANNEL** drives Na^+ Reabsorption in the principle cell.
            - Paracellular pathway does *not* occur appreciably, as these are tight epithelia.
            - **Amiloride** is a diuretic that will block this channel.
        - Cl^--REABSORPTION occurs concurrent with Na^+, but it is poorly understood how this occurs.
        - **ALDOSTERONE** stimulates Na^+ reabsorption and K^+ secretion in these cells -----> more net water reabsorption.
            - **Aldosterone Induced Proteins** are cytoplasmic receptors for Aldosterone (a steroid) ------> increase synthesis of Na^+ channels and possible increase Na^+ conductance.

            - K^+-Secretion effect is not as well understood, but stimulation of **Na/K-ATPase** plays a role.
            - The effect of Aldosterone is a *slow, long-lasting effect,* since Aldosterone is a steroid and regulates at the synthetic level.
        - **ADH:** *Principle cells are sensitive to ADH*.
            - ADH binds to **V_2-Receptors** on the basolateral membrane ------> G-Protein ------> cAMP ------> Induces insertion of **aggrephores** on apical membrane ------> higher water permeability.
            - ADH is a *short-term* regulator. Changes in plasma volume exert effects within 5-10 minutes.
    - **INTERCALATED CELLS:** Intercalated cells are found only in the cortical segment. These cells are important to potassium homeostasis.
        - H^+ and HCO_3^- Secretion.
            - **ALDOSTERONE** stimulates H^+ secretion in these cells.
        - K^+ Reabsorption and Secretion.
- DISTAL TUBULE REABSORPTION:
    - *Increased tubular flow rate ------> increased net reabsorption of salt.*
        - This is true because increased flow rate ------> more Na^+ is in the filtrate ------> reabsorption gradient remains high for a longer period of time ------> more resorption.
    - *Increased tubular flow rate ------> increased net reabsorption of water*. Water increases because salt increases.

COUNTER-CURRENT MECHANISM: The mechanism by which concentrated, hypertonic urine is created.

- The Na/Cl/K channel of the Thick Ascending Limb is the primary furnace for the counter-current multiplier.
- MEDULLA / LOOP OF HENLE: NaCl is trapped and recycled in the medulla:
    - Descending Limb: some of it leaks out to the tubular fluid.
    - Ascending Limb: It is actively kicked back into the tubular fluid, on a gradient-limited basis. Thus the higher the gradient, the more of it will be kicked out into the interstitium.
    - *The highest gradient is created at the very bottom of the loop, in the deepest part of the medulla*.
    - *The filtrate becomes even more hypotonic as it goes through the loop; the excess salt is deposited in the medulla*.
- DISTAL / COLLECTING TUBULES:
    - CORTICAL DISTAL CONV TUBULE: In the presence of ADH, it transports water into the **cortical** interstitium, as it receives an extremely hypotonic filtrate.
    - MEDULLARY COLLECTING TUBULES: It reaps the benefits from the counter-current multiplier. It can transport lots of water to create extremely hypertonic urine.
- **VASA RECTA:** The concentration of the blood plasma increases as the filtrate concentration increases in the medulla. Salt leaks into the vasa recta.
    - MEDULLA: Blood plasma has high osmolarity.
    - CORTEX: *As the plasma goes into the cortex, it's hyperosmolarity allows it to reabsorb any water that was transported from the Distal and Collecting Tubules*.
    - SALT-BALANCE: Salt leaks into the vasa recta in the medulla.
        - An equilibrium concentration of ISF salt is reached, where the rate of transport of salt into the medulla (TALH channels) is equal and opposite to the rate of salt leakage out into the vasa recta.
    - UREA: High concentration of urea in the medulla is essential for an effective counter-current multiplier.
        - Most of the urea comes from the **collecting tubule, inner medulla** (very end of the nephron). That's where urea passively diffuses into the medullar interstitium.

        - Sparing the detail, the countercurrent flow of the vasa recta help to keep the medulla high in urea concentration.
        - Ultimately, Urea concentration in the medulla depends on active salt-transport in the thick-ascending limb (just like all of the counter-current system depends on this).
- FACTORS THE ALTER THE COUNTER-CURRENT MECHANISM:
    - ANATOMIC: The longer (juxtamedullary) nephrons have a more powerful concentrating ability. They can create more concentrated urine.
    - ADH: Presence of ADH will cause reabsorption of water and a more concentrated urine. Its presence is required for effective countercurrent.
    - **FLUID FLOW RATE:** Maximum effectiveness occurs when the flow rate through the loop is high and through the collecting tubule is low.
        - A higher flow rate in the loop will *increase* active salt reabsorption.
        - A *lower flow rate* in the collecting tubules will tend to increase the effectiveness of the counter-current multiplier.
            - High collecting tubule flow rate ------> more water *initially* will flow into the medullary ISF ------> *the medullary ISF gradient will be ruined* and the net result is actually less water reabsorption.
    - UREA: Reduced supply of urea (via low dietary protein) can lessen the concentrating ability.
    - DIURETICS: The loop diuretics in particular practically wipe out the counter-current.

MEASUREMENT OF RENAL FUNCTION:

- **CLEARANCE:** The **Virtual Volume** of plasma containing a substance that was excreted in the kidneys, per unit time.
    - Clearance indicates the minimum volume that must have been filtered by the kidney, in order to account for the excretion of a substance in the blood.

$$Clearance = \frac{(Urine\ Conc) \times (Urine\ Vol)}{(Plasma\ Conc)} = \frac{U \times V}{P}$$

        - This is based on the Dilution Principle:
        - (Conc)(Volume) = (Conc)(Volume)
        - Total Amount = Total Amount
- **GLOMERULAR FILTRATION RATE (GFR):**
    - GFR can be measured as the Clearance of **Inulin**, $\mathbf{C_{In}}$
        - Inulin is neither secreted nor reabsorbed. Thus the inulin clearance is equal to the Glomerular Filtration Rate.

$$C_{In} = \frac{U_{In} \times V}{P_{In}}$$

    - INULIN is difficult to use because you must infuse the substance and then completely empty the bladder both before and after the infusion, to ensure full recovery.
    - INCREASE PLASMA CONCENTRATION of a substance that is strictly filtered ------> the amount filtered increases but the volume of filtrate doesn't change ------> **clearance remains constant**.
- TUBULAR TRANSPORT: The difference between what is filtered and what is excreted.
    - **TUBULAR REABSORPTION RATE:** If more is filtered than is excreted, than some of it was reabsorbed, or net reabsorption has occurred.

$$T_x = (GFR \times P_x) - (V \times U_x)$$

- ***Amount Reabsorbed = Amount Filtered - Amount Excreted***
- ***= (GFR)(Plasma Conc) - (Urine flow)(Urine conc)***
- INCREASE PLASMA CONCENTRATION of a reabsorbed substance ------> channels get saturated ------> relatively more is excreted ------> **higher net clearance**.

o **TUBULAR SECRETION RATE:** If more is excreted than filtered, than some of it was secreted, or net secretion has occurred.

- $T_x = (V \times U_x) - (GFR \times P_x)$
- ***Amount Secreted = Amount Excreted - Amount Filtered***
- ***= (Urine flow)(Urine conc) - (GFR)(Plasma Conc)***
- INCREASE PLASMA CONCENTRATION of a secreted substance ------> channels get saturated ------> relatively less is secreted ------> **lower net clearance**.

o **T_M, Maximum Rate of Transport:** In order to accurately measure it:

- You must saturate the transport system (plasma levels of the substance must be high enough)
- You must get two consecutive clearance measurements in which blood levels have risen but transport rate has not. This ensures you have reached the maximum T_M

- **RENAL PLASMA FLOW (RPF)**: The clearance of **Para-Amino Hippurate (PAH)**, C_{PAH}
  - PAH is very effectively cleared by **secretion** in the proximal tubule. 90% of PAH in the blood is secreted into the tubules and not reabsorbed. Because virtually all PAH is cleared per volume of blood, PAH clearance can be used as an estimate of RPF.
  - $$C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}}$$
  - RPF MEASUREMENTS: Clinically PAH basically cannot be used to measure Renal Blood flow in compromised patients.
    - Instead, inject a radioactive isotope into the plasma and watch it accumulate in the kidney.
    - How quickly the isotope leaves the blood (and enters the kidney) is a rough indicator of RPF. **RENAL BLOOD FLOW (RBF):** It equals renal plasma flow + the flow of red blood cells.

$$RBF = RPF + (RPF \times Hct) = \frac{RPF}{(1 - Hct)}$$

- The larger the hematocrit, the larger the renal blood flow.

- **CREATININE CLEARANCE:** Clinically Creatinine clearance is measured to estimate GFR, instead of Inulin clearance.
  - $$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$
  - NUMERATOR is falsely raised a little because some **secretion** of creatinine occurs in the kidney.
  - DENOMINATOR is falsely raised a little because of **non-creatinine chromogens** the react with the creatinine testing reagent, in the blood.
  - The two offset each other, so Creatinine clearance is generally considered to be a good indicator of GFR.
  - *Falsely high GFR values may be obtained with people who have good blood flow (RPF) but poor glomerular function (GFR)*.

- **FRACTIONAL EXCRETION**: The fraction of the filtered amount of a substance that the tubule excrete. This is a measure of **reabsorption capacity.** *The smaller the fractional excretion, the better the reabsorption capacity*.

Fractional Excretion of Water: $$FE_{H_2O} = \frac{1}{U_{Cr} / P_{Cr}} \times \frac{P_{Cr}}{U_{Cr}}$$

  - All you have to do is measure Creatinine in the blood and in the urine and take the ratio.
  - *The lower the Fractional Excretion of water, the better*. A low fractional excretion indicates that tubular reabsorption functions are working.

  - **FRACTIONAL EXCRETION of Any Other Substance:** $$FE_x = \frac{U_x / P_x}{U_{Cr} / P_{Cr}}$$
    - **You Pee / You Pee** is the mnemonic to remember this.
    - Again, higher fractional excretion indicates impaired tubular function.
  - **FRACTIONAL EXCRETION OF SODIUM:** $$FE_{Na} = \frac{U_{Na} / P_{Na}}{U_{Cr} / P_{Cr}}$$
    - FE_{Na} should be 1% - 3%. Anything higher than 3% indicates impaired tubular function.
    - **Diuretics**, of course, will falsely make this number a lot higher.
  - **FRACTIONAL REABSORPTION RATE = (1 - Fractional Excretion)** for any substance.
    - The higher the Fractional Reabsorption, the better.
- **PLASMA CREATININE CURVE:** High Plasma Creatinine means low creatinine clearance, which means trouble. *Taking the **reciprocal (1 / P_{Cr})** of P_{Cr} will tell you how a chronic patient is improving.*
  - If the reciprocal is decreasing rapidly over time, then the patients condition is worsening.
  - If the reciprocal is leveling off in its decrease, then the patient is slowly improving.

REGULATION of RENAL FUNCTION

UREA: It is freely filtered, and its reabsorption is dependent on urine flow rate.

- *The higher the urine flow rate, the less of it is reabsorbed*.
- Permeability to Urea occurs in two places:
  - PROXIMAL TUBULE: Some urea reabsorption occurs, but more water reabsorption occurs so urea filtrate concentration actually goes up.
  - INNER MEDULLARY COLLECTING TUBULE: Due to concentration prior to this point, a large gradient for Urea reabsorption occurs in this segment. *Urea is reabsorbed and concentrated into the interstitial medulla, where it plays an integral role in counter-current exchange*.
- **Uremia:** Renal failure makes urea accumulate in the blood. However, urea is not as toxic as some other metabolites that accumulate, so uremia toxicity usually isn't due to urea per se.

DIURESIS: An increase in water excretion.

- **Water Diuresis:** Increased water excretion without corresponding increase in salt excretion.
  - Primary cause = increased intake of water.
  - Increased water intake will cause plasma ADH levels to fall.
  - **Diabetes Insipidus** = water diuresis resulting from no ADH secretion (usually) or faulty ADH receptors.

    - *Water diuresis only exerts its effects on the distal tubules*. That's where ADH can exert influence.
        - Thus water diuresis fractional excretion never exceeds 8% - 11% of GFR.
- **Osmotic (Solute) Diuresis:** Increased water excretion concurrent with increased salt excretion.
    - Causes:
        - Massive increase in salt present in the tubular fluid.
        - Diuretic drugs ------> inhibited reabsorption
    - *Solute diuresis can act at any specific site where reabsorption is impaired or inhibited.*

REGULATION OF PLASMA OSMOLARITY:

- **ADH-SECRETION:** Primary mechanism that respond to plasma *osmolarity.*
    - Produced in **Supraoptic** and **Paraventricular Nuclei** of Hypothalamus ------> Posterior Pituitary
    - FEEDBACK MECHANISM:
        - STIMULUS: *Rise in ECF Osmolarity ------> ADH Secretion from posterior pituitary*.
            - **Osmoreceptors** in the hypothalamus sense an increase in plasma osmolarity.
            - The range over which the receptors operate is a very strict, sensitive range.
                - BASAL ACTIVITY: **280 mOsm / kg** ------> **0.5 pg / mL** ADH.
                - MAXIMAL SECRETION: **295 mOsm / kg ------> 4.0 pg / mL** ADH
            - Effective stimuli for ADH release are **NaCl** and Mannitol -- NaCl and water loss are the most important stimuli.
                - Urea is not an effective stimulus.
                - Blood glucose is not an effective stimulus when insulin is present. In the absence of insulin there is a small effect.
        - FEEDBACK: Plasma Osmolarity ------> ADH ------> Water Reabsorption ------> Plasma Volume ------> Plasma Osmolarity
- DIURESIS: 70 kg person ingests 1L of water ------> 28% (280 mL goes to plasma) ------> very small decrease in plasma osmolarity.
    - This effect is not enough to alter GFR.
    - This effect *is enough* to reduce ADH secretion in posterior pituitary.
- ADH DISORDERS:
    - **DIABETES INSIPIDUS:**
        - Primary Insufficiency of ADH is the most common cause.
        - **Nephrogenic** Diabetes Insipidus is inability for kidney to respond to ADH.
        - **Psychogenic** Diabetes Insipidus is compulsive water-drinking (polydipsia).
    - **SIADH:** Syndrome of Inappropriate Secretion of ADH. Excessive ADH secretion.

REGULATION OF PLASMA VOLUME:

- **ATRIAL RECEPTORS:** Stretch receptors in the Right and Left Atria that respond to *high plasma volume*.
    - STIMULATE Atrial Receptors ------> Fire Vagus Nerve ------> Multiple end-effects.
        - Suppression of ADH release in hypothalamus.
        - Decreased Sympathetic Outflow ------> arteriolar vasodilation ------> higher capillary hydrostatic pressure ------> edema (fluid moves out of vascular space and into interstitium).
        - Decreased Sympathetic Outflow ------> less Renin from kidney.
    - **ATRIAL NATRIURETIC FACTOR (ANF)** is also released when the stretch receptors are stimulated (but not via Vagus). ANF generally works to reduce blood volume.
        - ANF will cause further arteriolar vasodilation ------> edema.

        - ANF inhibits Aldosterone in the Adrenal Cortex.
- **BARORECEPTORS:** They will decrease sympathetic outflow ------> less Renin.
    - They can also inhibit ADH secretion.
- **JUXTAGLOMERULAR APPARATUS:**
    - TWO STIMULI (INPUTS):
        - Arterial Pressure Changes (Afferent Arteriole)
        - Rate of flow of tubular fluid (i.e. rate of delivery of salt) in Macula Densa of the DCT.
    - MULTIPLE RESPONSES (OUTPUTS)
        - Sympathetics can influence the JGA by resetting the set-point of tubulo-glomerular feedback ------> Alter arteriolar constriction and perhaps mesangial cell constriction.\
- SYMPATHETICS: *An increase in sympathetics will result in more water retention, via peritubular capillaries, in the kidney and will result in a* ***higher filtration fraction***.
    - Sympathetics ------> ------> GFR / RBF ratio ------> capillary oncotic pressure ------> *more water reabsorption*.
        - This is a direct JGA effect, as well as via Renin and Angiotensin (see below).
    - Sympathetics ------> ------> GFR / RBF ratio ------> Capillary oncotic pressure ------> *more water excretion*.
    - alpha-RECEPTORS:
        - Vasoconstriction in the efferent arteriole.
        - alpha-receptors are on the proximal tubules to promote Na^+ reabsorption.
    - beta-RECEPTORS: beta-Receptors are on granule cells to promote renin release.
- **RENIN / ANGIOTENSIN SYSTEM:** Renin ------> Angiotensin I ------> Angiotensin II
    - Three pathways for controlling Renin Secretion:
        - **INTRARENAL BARORECEPTOR:** In the afferent arteriole, a fall in pressure -----> direct stimulation of renin release in granule cells.
        - **SYMPATHETIC INPUT:** Neural (NorE) and Humoral (Epi) input to the JGA stimulates rein release.
            - **beta-Receptors on Granule cells** respond to both NorE and Epi to release Renin.
            - Atrial Stretch Receptors are believed to be the major sensors involved in this pathway -- not the baroreceptors.
        - **MACULA DENSA FEEDBACK:**
            - Reduced tubular fluid flow (reduced delivery of salt to macula densa) -----> stimulate release of Renin.
    - **ANGIOTENSIN II:** Potent vasoconstrictor
        - It stimulates release of Aldosterone.
        - It stimulates $NaHCO_3$ reabsorption in the proximal tubule ------> more water reabsorption.
        - It preferentially constricts the efferent arteriole ------> capillary pressure and RPF ------> GFR / RPF ratio (i.e. RPF decreases more than GFR).
        - *The result of this is that the peritubular capillary* ***oncotic pressure, PI_b,*** *increases* ------> more water reabsorption in proximal tubule.
- **ALDOSTERONE:**
    - Its release is stimulated by Angiotensin II and K^+ in blood.
    - It promotes Na^+ reabsorption and K^+ excretion in distal tubule.
- **ADH**: ADH also responds to low blood volume (blood pressure) directly. This response is much less sensitive than the response to osmolarity.
- **ATRIAL NATRIURETIC FACTOR:** It reduces blood volume by increasing the excretion of salt and water (mechanism unknown).
    - It is known to supress Aldosterone secretion, and it may supress renin secretion too, but the evidence is conflicting.

SEVERE VOLUME DEPLETION: Summary of volume effects

- MAJOR STIMULI:
  - Increased plasma osmolarity
  - Decreased blood volume (atrial receptors)
  - Decreased blood pressure (baroreceptors)
- MAJOR OUTPUT
  - SYMPATHETICS
  - Increase in Renin / Angiotensin / Aldosterone system
- KIDNEY: Reduced excretion of salt and water; increased retention.

ACUTE VOLUME EXPANSION: Summary of volume effects

- MAJOR STIMULI: Change in atrial volume (volume receptors) and atrial pressure (baroreceptors)
- MAJOR OUTPUTS:
  - **Atrial Natruretic Factor** is probably the most significant positive response.
  - Decreased Sympathetics
- KIDNEY: Massive diuresis and dilute urine

ACID-BASE BALANCE: Usually, net secretion of acid occurs (we have an acidic diet).

- **PROXIMAL TUBULE:** HCO_3^- is the predominant buffering system acting.
  - **Na^+/H^+ ANTIPORT** is stimulated by an acidic (less than 7.4) pH ------> secrete more acid.
    - It is inhibited by a basic (greater than 7.4) pH ------> secrete less acid.
  - **HCO_3^- REABSORPTION** occurs in the proximal tubule to the greatest extent (about 75%)
  - However, because it is a low gradient system, it still does not affect the tubular fluid pH that much.
- DISTAL TUBULE: NH_3 and HPO_4^{-2} are the predominant buffering systems.
  - **ACID PUMP: H^+-ATPase** secretes protons into the tubular fluid.
    - These pumps are located in **alpha-intercalated cells** in the distal tubule.
    - Transporters that balance the H^+ pump:
      - **Cl^-/HCO_3^- ANTIPORT** gets rid of the excess HCO_3^- created by this proton pump. It pumps the HCO_3^- out into the blood and Cl^- into the cell.
      - **Cl^--Channel**, finally, then recycles the Cl^- back out into the blood as well.
    - REGULATION OF BLOOD pH: **Blood PCO_2 ------> H^+ concentration in cytoplasm of tubular cells ------> H^+ secretion**.
    - ELECTROCHEMICAL GRADIENT: *The H^+ pump is limited by the electrochemical gradient.*
      - H^+ in tubular fluid ------> hyperpolarize apical membrane ------> turn off pump.
      - The limit of H^+-excretion by this pump is reached at a tubular pH of about 4.5
  - **BASE PUMP: Cl^--HCO_3^- ANTIPORT** pumps HCO_3^- into the tubular fluid.
    - **beta-Intercalated Cells** are the names of the cells that secrete base.
    - *This is the exact reverse of above*. The H^+-ATPase pump is then put on the basolateral membrane to counteract the HCO_3^- pump.
  - OVERALL CAPACITY: The distal tubule can secrete very acidic urine. However, the presence of any HCO_3^- in this segment will lessen its ability to secrete acid as the non-bicarbonate buffers become weaker.
- **TUBULAR FLUID BUFFERS:** An increase in the amount of buffers in the tubular fluid will increase the rate of H^+-Secretion. *All secreted protons must be buffered in the tubular fluid*.
  - **BICARBONATE H_2CO_3 : HCO_3^- BUFFER:** Base reabsorbed in the form of HCO_3^-. *This mechanism predominates in the proximal tubule*.
    - BUFFERING PROCESS:

        - H^+ reacts with HCO_3^- in tubular fluid ------> $CO_2 + H_2O$
        - CO_2 then comes back into the cell.
        - Inside the cell, the CO_2 reacts with H_2O and **Carbonic Anhydrase** to reform HCO_3^-
        - HCO_3^- is then excreted into blood.
        - NET RESULT: Movement of one HCO_3^- from the tubular fluid to the blood ------> net excretion of acid.
    - **PLASMA HCO_3^- CONCENTRATION** determines the filtrate HCO_3^- concentration, which determines how much buffering capacity the filtrate will have.
        - FEEDBACK: Plasma [HCO_3^-] ------> Filtrate [HCO_3^-] ------> H^+-secretion and higher blood pH.
        - **Plasma [HCO_3^-] below 24 mEq/L:** Almost all HCO_3^- will be reabsorbed to keep HCO_3^- levels in blood higher.
        - **Plasma [HCO_3^-] above 24 mEq/L:** *Both reabsorption and excretion of HCO_3^- increase, but excretion increases even more* ------> net excretion of HCO_3^-
  - **PHOSPHATE HPO_4^{-2} : $H_2PO_4^-$ BUFFER**: Acid excreted in the form of $H_2PO_4^+$. *This mechanism predominates in the distal tubules*.
    - When HPO_4^{-2} picks up an H^+, it is still negatively charged afterward, which means it remains lipid-insoluble and it must be excreted.
    - This is a non-bicarbonate buffer and is responsible for acid secretion. The rate of acid-secretion will be proportional to the strength of this buffer.
  - **AMMONIA NH_3 : NH_4^+ BUFFER:** Acid excreted in the form of NH_4^+. *This mechanism predominates in the distal tubules*.
    - As above, once NH_3 accepts a proton to become NH_4^+, it is charged and lipid-insoluble, and thus it must be excreted.
    - This is a non-bicarbonate buffer and is responsible for acid secretion. The rate of acid-secretion will be proportional to the strength of this buffer.
    - KIDNEY PRODUCTION of AMMONIA: **GLUTAMINASE** provides the kidney with the majority of ammonia that it excretes. It will yield ammonia + Glutamate, from Glutamine. Further deamidation of glutamate (to alpha-ketoglutarate) also provides some ammonia.
        - Both these rxns occurs in tubular cell mitochondria.
    - **NH_4^+** can also be actively transported in place of H^+ in the Na/H antiport, and in place of K^+ in the K/Cl/Na loop transporter.
- **ACID-EXCRETION: NON-BICARBONATE BUFFER CONCENTRATION** ultimately determines the ability of the kidney to excrete acid!
  - **Plasma HCO_3^- Concentration**: High plasma HCO_3^- ------> High filtrate HCO_3^- concentration ------> the HCO_3^- buffer becomes relatively stronger than the NH_3 and HPO_4^- buffers in the tubular fluid ------> *less acid excretion*.
  - **Blood PCO_2:** High blood PCO_2 ------> ------> *greater acid excretion* by two different mechanisms.
  - SUMMARY: **Low blood HCO_3^- and high blood PCO_2 both lead to greater acid excretion**.
- **CARBONIC ANHYDRASE:** It maintains a constant pH within tubular cells.
  - **ACETAZOLAMIDE** inhibits Carbonic Anhydrase ------> less H^+ secretion in proximal tubule (inhibit Na^+/H^+ antiport) *and less Na^+ reabsorption* ------> **diuresis**.
    - Acetazolamide is thus a diuretic that acts by inhibiting carbonic anhydrase.
    - Continued use will cause secretion of an alkaline urine and will result in acidosis.

COMPENSATED RESPIRATORY ACIDOSIS: Example of kidney acid-base regulation.

- HYPOVENTILATION ------> PCO_2 ------> [HCO_3^-] ------> pH
- The higher PCO_2 in tubular cells stimulates the secretion of acid. This will correct for the acidic pH but not the plasma HCO_3^- concentration.

- OVERALL: Chronic Hypoventilation, as in COPD.
    - pH near normal 7.35
    - HCO_3^- extremely high 34-36 mEq/L
    - PCO_2 high (hypercapnia) 60 mm Hg

METABOLIC ALKALOSIS: As from chronic vomiting.

- RESPIRATORY RESPONSE is chronic hypoventilation ------> pH is completely corrected but a *higher HCO_3^-* results.
- KIDNEY RESPONSE: plasma [HCO_3^-] ------> HCO_3^- in filtrate ------> both excretion and reabsorption of HCO_3^- increase, but excretion increases more ------> net alkaline urine is created.

POTASSIUM HOMEOSTASIS: The kidney is the main organ responsible for potassium balance.

- EXTRARENAL MECHANISMS:
    - **Insulin** stimulates Na/K-ATPase in liver and muscle ------> K^+ uptake
        - This is a mode of absorbing dietary potassium, in the absorptive state.
    - **Aldosterone** acts on extrarenal tissues to increase K^+ cellular uptake, but this is a slow mechanism.
    - **Catecholamines (beta2)** indirectly stimulate Na/K-ATPase
    - **Acidosis** ------> blood K^+ by shifting K^+ to the ECF because of the shift in electrochemical gradient.
- KIDNEY
    - **REABSORPTION:** *Over 90% of filtered K^+ is reabsorbed.*
        - PROXIMAL TUBULE (65-70%): Mechanisms are not completely understood here; much probably occurs via paracellular diffusion.
        - LOOP of HENLE (20%): Na/K/Cl transporter.
    - **SECRETION:** Basically *all K^+ in the urine came from secretion in the distal and collecting tubules*.
        - **PRINCIPLE CELLS** in the DCT and COLLECTING TUBULES: They secrete K^+.
- Factors affecting K^+ Secretion:
    - **Plasma K^+ concentration** directly drives the Na/K-ATPase ------> more K^+ into Principle cells ------> more K^+ secretion.
    - **ALDOSTERONE** promotes K^+ secretion in the principle cells.
        - It is thought to do this by stimulating production of the Na/K-ATPase pumps.
        - Again, this is a long term-effect.
    - **ADH** raises K^+ permeability to stimulate secretion. Effect not as significant as Aldosterone.
    - **Alkalosis** increases K^+ membrane conductance in apical channels by increasing the pH of the tubular fluid.
    - **DIURETICS** have important effects on K^+ secretion. They potentially lead to **hypokalemia** which is an unwanted side-effect of diuretics.
        - Carbonic-Anhydrase Inhibitors are potent stimulators of K^+-secretion.
        - Thiazide diuretics increase tubular fluid flow rate and thus K^+ secretion.
        - Loop diuretics increase K^+ excretion because they inhibit K^+ reabsorption.