- OSMOLARITY: Refers specifically to the concentration of all *impermeable* particles across a membrane.
    - ISOOSMOLAR: A **300 mOsm** solution is the same as normal body osmolarity, both intracellularly and extracellularly.
    - HYPER / HYPO OSMOLAR: Having higher or lower concentration of impermeable solutes across a membrane.
- TONICITY: Refers specifically to the movement of water into or out of a cell.
    - HYPERTONIC CELL: Having a higher osmolarity inside, such that water will come in the cell and the cell will swell.
    - HYPOTONIC CELL: Having a lower osmolarity inside, such that water will leave the cell and the cell will shrink.
    - If you put a cell in a HYPERTONIC SOLUTION, it's the opposite -- water will leave the cell and the cell will shrink.
    - If you put a cell in a HYPOTONIC SOLUTION, water will come in and the cell will swell up.

SHIFTS OF BODY WATER:

- If you add an ISOTONIC solution to the body, all (most) the water will remain in the extracellular spaces, as you have not changed the concentration gradient and there will be no net movement of water after addition of the new fluid.
- Add a HYPOTONIC solution, and water will move into the intracellular spaces.
- Add a HYPERTONIC solution, and you will draw additional water out of the intracellular spaces into the extracellular space.
- Principles:
    - Over the whole body, water moves rapidly to equilibrate any osmolarity difference between extracellular and intracellular spaces.
    - Unless solute is added or removed, the amount (but not necessarily concentration) of solute in a compartment remains constant.
    - Sodium and Chloride are confined to the extracellular space.
    - In an equilibrated system, the movement of water will follow the movement of solute into or out of cells.
- *At equilibrium, pure water is distributed to body compartment according to the total solute content in each compartment*.
    - So, if we have 50% of all impermeable solutes in the extracellular spaces and 50% in the intracellular spaces. Then 50% of total volume after addition will be in each respective space after equilibrium.

COMMON ION CONCENTRATIONS:

ION	Intracellular Conc	Extracellular Conc
K^+	140 mOsm -- high	4 mOsm -- low
Na^+	10 mOsm -- low	145 mOsm -- high
Cl^-	4 mOsm -- low	105 mOsm
Ca^{+2}	**Virtually zero**	2.5 mOsm -- pretty low

EQUIVALENTS: Moles of charge. 1 Molar solution of Ca^{+2} = 2 equivalents of Calcium.

MEMBRANE PERMEABILITY:

- Small ions (Na^+ and K^+) have very limited permeability through the membrane directly, i.e. through small, transient, water-filled holes in the membrane. They are not completely impermeable.
- DIFFUSION: Movement of a substance with its concentration gradient, due to *random thermal motion over time.*
- **FLUX =** the amount of solute that crosses a given area in a given amount of time, in **millimoles /cm^{2}sec**.
    - The flux is proportional to, and has the opposite sign of, the electrochemical gradient.

    - 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*.

- **CREATININE CLEARANCE:** Clinically Creatinine clearance is measured to estimate GFR, instead of Inulin clearance.
    - 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:

        - 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:**
        - **You Pee / You Pee** is the mnemonic to remember this.
        - Again, higher fractional excretion indicates impaired tubular function.
    - **FRACTIONAL EXCRETION OF SODIUM:**
        - 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 patient's 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.