# <u>Homeostasis, Body Fluids, and Transport Mechanisms</u>

**Objectives:**

- Homeostasis
- General Characteristics of Homeostatic Control Systems
  - Feedback Systems
  - Resetting of Set Points
  - Feed-Forward Regulation
- Components of Homeostatic Control System
  - Reflexes
  - Local Homeostatic Responses
- Body Fluid Compartments
  - Diffusion
    - Magnitude and Direction of Diffusion
    - Diffusion Rate Versus Distance
    - Diffusion Thorough Membranes
  - Mediated-Transport Systems
    - Facilitated Diffusion
    - Active Transport
  - Osmosis
    - Extracellular Osmolarity and cell volume
  - Endocytosis and Exocytosis
  - Epithelial Transport

**The Challenge**:

- Why do you need to know understand physiology?
  - To help you decide what is fact and what is fiction

- What if someone tells you that (Junk) food makes your blood acidic and that their doctors told them that their blood was pH 6.0?

**Clinical Problem:**

- George sets off on a long training run on a hot and humid Sunday morning. Two hours later you discover him lying at the roadside in a state of confusion and delirium. His skin is hot and dry. He is hyperventilating and his heart rate is increased.
  - What is George's problem
  - What should you do ? How do you help him ? Should you give him Water? Gatorade? A large double double?
  - Or, do you use your iPhone to search the web to figure out what to do, to call 911 and then play solitaire until help arrives ?
  - Or, do you push him to the side of the road so that others dont run him over like you just did because you were texting while driving.
  - Do you have enough knowledge to understand the problem and know what to do? What is the underlying physiological problem
- Suffering of a heatstroke

**This is a problem of "Clashing demands":**

- Most common physiological variables found in normal, healthy organisms are maintained within a predictable range (e.g. blood pressure, body temperature, and blood oxygen, glucose and sodium). This gave rise to the concept that of a constant internal milieu is required for good health.
- The term ‘’ homeostasis’’ was coined by Walter Cannon, an early twentieth century physiologist, to describe the ability of the body to maintain relatively stable internal conditions even though the external environment changes continuously.
- Homeostasis is not ¨static¨ as the name implies

- It is dynamic

- Homeostasis refers to the dynamic mechanisms that detects and responds to deviation in physiological variables from their ¨set point¨ values by initiation effector responses that retires the variables to the optimal physiological range.
- How are these limits maintained ? What can go wrong?

**Homeostasis: A defining feature of Physiology:**

- Homeostasis is one of the unifying concepts of physiology. Even though the system of the body are presented in discrete chapters they are all linked by their real in maintaining the constant internal environment of the body. The function of organ systems is to maintain a stable internal environment.
  - Homeostasis does not imply that a given physiological function or **variable** is rigidly constant but rather that it fluctuates within a predictable and often narrow range. When disturbed up or down from the normal range, it is restored to normal.
  - Thus, homeostasis is a state of **dynamic constancy.** A variable like blood glucose may vary in the short term, but is fairly constant when averaged over the long term.

**Homeostasis…:**

- It is important to realize that a person may be homeostatic for one variable but to for another. For example, blood Na+ may be normal but may have abnormally high carbon dioxide levels resulting form a long disease.
- Numerous physiological variables must be maintained homeostatically. Dramatic changes in just one variable can have life-threatening consequences.
- When homeostasis is lost for one variable, it <u>may</u> trigger a series of changes in other variables.
- Certain diseases or illnesses can be characterized as a loss of homeostasis in one of more system in the body ( homeostatic imbalance).
  - Diseases can be considered out of homeostasis

**General Characteristics of Homeostatic Control Systems:**

- A **steady state** is defined as a system in which a particular variable is not changing, but energy must be added continuously to maintain a constant condition.
- It differs from **equilibrium,** in which a particular variable is not changing but no input of energy is required.
- The **set point** is the numerical value of the variable measured at steady state.
  - Value you want to maintain
- Stability of an internal environmental variable is achieved by the balancing of **inputs** and **outputs**.
- In a **negative feedback** control system, a change in the variable being regulated brings about responses that tend to push the variable in the direction opposite to the original change. Negative feedback minimized changes from the set point of the system leading to stability.
- **Positive feedback**, which accelerates a process, is less common because it pushes values away from the set point.

**Myth or Fact:**

- Problem: Your friend tells you that St.Bernard rescue dogs carry casks of brandy because the alcohol enables a hypothermic person to survive longer.
- You know its likely untrue, but do you convince your friend? How of you approach a such problem?

**A strategy for analyzing homeostatic responses:**

- Identify the internal environmental variable.
  - Body temperature
- Establish the ¨set point¨value for that variable.
  - 36.8 +/- 0.7 °C

- Identify the inputs and outputs affecting the variable.
    - External temperature, physical activity, time of day, **alcohol**
- Examine the balance between the input and outputs.
    - Losing heat to the environment too quickly
- Determine how the body monitors/ senses the variable.
    - Temperature sensitive nerve endings
- Identify effectors that restore the variable to its set point.
    - Shivering , the main way a body generates heat

*In hypothermia, the body temperature drops below that required for normal metabolism and bodily functions. In humans, this is usually due to excessive exposure to cold air or water but it can be deliberately induces as a medical treatment. Symptoms usually appear when the body's car temperature drops by 1-2°C below normal.*

**MythBusters to the rescue:**

- To test this myth, Adam and Jamie swallowed internal thermometers which contained tiny transmitters that sent their core body temperature to a digital display. They also used a thermographic camera to record the temperature of each others' face and hands. After receding their temperature at RT, they went to a frozen food warehouse and sat in a room kept at 0°F ( -18°C).
- Not long after entering in the room, they started feeling the heat leave their extremities and measured their temperature again. They discovered that while their face and hands were indeed much colder, their core body temperature were actually higher than when they were outside the freezer.
- They then called Bob, a St.Bernard carrying a cask of brandy. Adam and Jamie drank the brandy and measured their temperatures again. They discovered their face and hands were warmer but their core body temperature were dropping fast.

Adam and Jamie declared the myth busted for this reason. They did, however, find some positive effects from drinking the brandy: alcohol caused their blood vessels to widen, resulting in more blood going to the extremities, and lowering the risk of getting frostbite. They also reported that they felt a lot better after drinking.

- In conclusion, they erased that if rescue was imminent, it would be a good idea to drink the brandy, but if rescue was uncertain, it would be a bad idea to drink alcohol because it would make you die more quickly. They also noted that the phenomenon of St.Bernard roaming the mountains with casks of brandy itself a myth.

**Components of Homeostatic Control Systems:**

- Usually multiple systems (organs) control a singles variable. Homeostasis requires communication between these different organ system. Signals are relayed mainly by the nervous system and by the endocrine system (hormones).
- Homeostatic control mechanism are examples of reflexes.
- A *reflex* is an involuntary (built-in) response to a particular stimulus.
- Many reflexes occur without out awareness. Many responses appear automatic but are the result of leaning (*acquired reflexes)*
- A pathway describing a reflex is known as a *reflex arc*.
- What components do you need to control a variable process?
  - Afferent : to the brain
  - Efferent : away from the brain

**Components of a Reflex Arc Regulating Body Temperature :**

The components of a reflex arc includes receptor, afferent pathway, interlarding centre, efferent pathway, and effector. The pathways may be neural or hormonal. Because so many properties of the internal environment are closely interrelated, it is often possible to keep one property relatively constant only by moving others away from their usual set point. This is referred to as competing or "clashing demands"

**What about poor George?**

- George sets off on a long training run on a hot and humid Sunday morning. Two hours later you discover him lying at the roadside in a state of confusion and delirium. **His skin is hot and dry**. He is hyperventilating and his heart rate is increased.
  - His skin is hot and dry - what does this mean? Normally, you perspire to help maintain body temperature homeostasis. But the water lost in perspiration leads to imbalance of total body water
    - Probably lost sweat meaning lost the body's way of cooling the body temperature down.
  - He is not sweating. Why not? Where does sweat come from? We need to know more about fluid compartments in the body.
  - What does sweat consist of? It is water only? Water and Salts? Should we give George gatorade? Or maybe he needs an IV?

**Body Fluid Compartments:**

- Water is present within and around all cells and within all blood vessels.
- Collectively, the fluid present in the blood (**plasma**) and between cells (**interstitial fluid**) is called extracellular fluid (ECF)
- The ECF consists of 20-25% plasma and 75-80% ISF
- In the capillaries, there is exchange of oxygen, nutriments, wastes, and other metabolic products between the plasma and the ISF, so the concentration of most dissolved substances are the same in both compartments (except protein). Therefore, the ECF is essentially homogeneous in composition.

- The composition of the intracellular fluid (ICF) is much different as we will see.
- Water accounts for 55-60% of normal body weight and is the major component of body fluids.
- Fluids are enclosed in compartments, which are defined and maintained by barriers - the properties of the barriers determine which substances can move between compartments. These movements account for the differences in composition of the fluids in the compartments.

**Movement of Molecules Across Cell Membranes**

- The contents of a cell are separated from the surrounding ECF by a lipid bilayer - the plasma membrane.
- The plasma membrane's role is to maintaining the crucial differences in the fluid composition of the cytosol and the extracellular fluid.
- The plasma membrane acts as a selective barrier, certain substances pass through easily, others are prevented from crossing.
- There are several mechanisms by which substances pass through membranes.
- The movement of molecules from one location to another solely as a results of their random thermal motion is known as **diffusion**.

**Diffusion:**

- Molecules of solute in a solution diffuse from a higher concentration to a lower concentration.
- The amount of material crossing a surface in a unit of time is know as a **flux**.
- The **net flux** between two compartments at any instant is the difference between the two one -way fluxes. The net flux always proceeds trim a higher concentration to a lower concentration (**downhill**)

- If the fluxes are equal in magnitude, but opposite in direction, then the net flux will be zero. The system is said to have reached **diffusional equilibrium**

**Magnitude and Direction of Diffusion:**

- The **net flux** is proportional to :
  - The concentration difference
  - Temperature (kinetic energy)
  - Molecular mass ( inversely)
  - Surface area between compartments
  - The medium through which the molecules are moving
- Diffusion times increase in proportion to the square of the distance over which the molecules diffuse, so it is only useful over short distances.
  - One-way fluxes can never be zero unless reached the temperature of absolute zero

**Diffusion through Membranes:**

- Diffusion rates across membrane are $10^3$-$10^6$ times slower than through a water layer of equal thickness.
- The magnitude of the net Flux (J) is directly proportional to the concentration difference across the membrane ($C_0$-$C_1$), the membrane surface (A), and permeability coefficient (P): $J = PA (C_0-C_1)$
  - Do not need to calculate the net Flux. This equation is just for understanding
- The lipid bilayer acts as a barrier to the passage of polar or changed molecules but non-polar (lipid soluble) molecules diffuse rapidly across membranes (drug design, metabolic intermediates).
- Some integral membrane proteins form channels that allow ions to diffuse across the membrane.

- Ion channels show <u>selectivity</u> for a particular type(s) of ion (for example, $Na^+$ and $K^+$)-based on channel diameter, charged residues lining pore, water of hydration.

**Role of Electrical Forces in Ion Movements:**

- The unequal distribution of ions induces a separation of electrical charges across the plasma membrane - called the **membrane potential** (electrical force).
- The direction and magnitude of ion fluxes across membranes depends on both the concentration <u>AND</u> the membrane potential. There two driving forces are collectively known as the **electrochemical gradient**. These forces may oppose each other.
- The inside of the cell has a net negative charge.

**Regulation of Diffusion Through Ion Channels:**

- Ions channels can exist in open or closed state. The process of opening and closing channels is known as channel grating.
- For a given electrochemical gradient, the number of ions that are conducted by the channel depends on:
  - How often the channel opens
  - How long it stays open
- Three kinds of grated channels:
  - Ligand-gated (Ions)
  - Voltage-gated (charges)
  - mechanically - gated (stimulation)
- A given ion may pass through several types of channels
- A given membrane may possess many different channel type and subtypes.

**Carrier-mediated transport:**

- Integral membrane transport proteins move solutes via conformational changes.
- Three factors determine the magnitude of solute flux through a mediated transport system
  - The extend to which the binding sites are "saturated"
  - The number of transporters in the membrane
  - The rate at which the conformational change occurs
- There are many types of transporters specific for a substance or class of substances (amino acids, glucose)
- Typically transpire fewer molecules per unit time than ion channels
- Two types of mediated transport
  - Facilitated diffusion
  - Active transport (Requires energy thus ATP)

**Facilitated Diffusion and Active Transport:**

- In **facilitated diffusion** the net flux proceeds across a membrane from higher to lower concentration.
- In **simple diffusion**, flux is limited only by the concentration gradient
- In carrier-mediated transport, flux depends on the number of available carriers
- The net movement of solutes from a lower concentration to a higher concentration requires the continuous input of energy from ATP
- There are two means of coupling ATP to active transport
  - The direct use of ATP in **primary active transport** (use of ATPase pump)
  - The use of an electrochemical gradient to drive **secondary active transport**

**Primary Active Transport:**

- The hydrolysis of ATP provides the energy for primary active transport
- Transporters are **ATPase** - enzymes that hydrolyze (break down using water) ATP
- Exemple: **$Na^+/K^+$ - ATPase pump**
  - The transporter (with bound ATP) binds 3 $Na^+$ on inside of cell (low affinity for $K^+$)
  - ATPase activated. Auto-phosphorylation
  - Conformation change and release of $Na^+$ to outside
  - Increased affinity for $K^+$ allows two $K^+$ to binds.
  - Dephosphorylation and return to original conformation. Release of $K^+$ to inside.
  - 3 $Na^+$ gets sent out of the cell meanwhile 2 $K^+$ gets sent inside the cell.

**The $Na^+/K^+$ - ATPase establishes electrochemical gradient:**

- The pumping activity of the $Na^+/K^+$ - ATPase establishes and maintains the characteristic distribution of high $K^+$ and low $Na^+$
- $Na^+/K^+$ -ATPase activity results in net transfer of positive charge to the outside of the cell, making the inside more negative.
- Thus, the $Na^+/K^+$ -ATPase establishes an electrochemical gradient that :
  - Can be used to do work ( transport of other solutes, for example)
  - Is the basis for electrical impulses in neutrons
- Between 10 and 40% of the ATP a cel produces under resting condition is used by the $Na^+/K^+$ -ATPase pump to maintain the sodium (and potassium) gradient

**Secondary Active Transport:**

- The energy stored in a electrochemical gradient can be used to drive the transport of other solutes.
- In **secondary active transport**, the movement of an ion done its electrochemical gradient is coupled to the transport of another molecule (ex. Glucose, amino acids)
- These transporters have binding sites for an ion (usually $Na^+$) and the cotransported molecule
- Thus, secondary active transport uses the stored energy of an electrochemical gradient to move <u>both an ion and a second solute</u> across a membrane. The creation of the electrochemical gradient, however, depends on primary active transporters.

**Symporters and Antiporters:**

- In secondary active transport, the movement of $Na^+$ is always downhill form [high] to [low]
  - **Cotransport (symport)** : the ion and the second solute cross the membrane in the same direction
  - **Counter transport (antiport)** : The ion and the second solutes move in opposite directions.

**Osmosis:**

- Water is a polar molecule that rapidly diffuses across the plasma membrane of most cells
- Facilitated by water channels called aquaporins ( Nobel prize awarded to Peter Agre in 1992 for their discovery). Aquaporins selectively conduct water

molecule in and out of the cell, while preventing the passage of ions and other solutes

- The water pores are completely impermeable to charged species, such as protons, a property critical for the conservation of the membrane's electrochemical potential.
- <u>Net diffusion of water across a membrane</u> is called **osmosis.**
- Water moves from [high] to [low]
- A litre of pure water (M.W.=18g/mol) weighs 1000g therefore concentration = 1000/18 = 55.5 mol/L or 55.5 M
  - No calculation on exams
- The addiction of solute lowers the water concentration **This depends on the number solute particles, not the chemical nature of the solute**

**Osmolarity:**

- The total solute concentration of a solution is known as its **osmolarity**.
- One osmol is equal to 1 mol of solutes particles.
  - 1 M solution of glucose = 1 Osm (1 osmol/L)
  - 1 M solution of NaCl = 2 Osm
  - 1 M solution of $MgCl_2$ = 3 Osm
  - A 3 Osm solution may have 1 mol glucose and 1 mol NaCl
    - Or any combination, once molecule is in water, it splits and the number of atoms in each molecule gives the Osm level.
- The higher the osmolarity, the lower the water concentration.
- Solutions with the same osmolarity have the same [water]
  - Volume does not change, The molecules switch places thus volume stays the same

**Osmotic Pressure:**

- When a solution containing solutes is separated from pure water by a semi-permeable membrane (permeable to water but not solutes), the pressure that must be applied to the solution (or compartment) to prevent the net flow of water into its is termed the **osmotic pressure**
- (imagine you are squeezing a ballon trying to prevent someone from blowing it up further)
- The greater the osmolarity of a solution, the greater its osmotic pressure and the lower its water concentration.
  - Volume changes because the impermeable membrane to the solutes wont allow the solutes to switch places with the water. Thus the volume of the container containing a higher concentration gradient will get higher and the volume of the container containing a lower concentration gradient will get lower.

**Extracellular Osmolarity and Cell Volume**

- $Na^+$, $Cl^-$, $K^+$ and proteins behave as **non-penetrating solutes**
- Osmolarity of ECF is ~ 300 mOsm
- Because water can diffuse across plasma membrane, osmolarity of ICF is also ~ 300 mOsm
- Changes in extracellular osmolarity can cause cells to shrink or swell
- The terms hypertonic, isotonic and hypotonic refer to solutions of without regard to weather the solute is penetrating (p) or non-penetrating(np)
- 1 L solution of 300 mOsm NaCl (np) and 100 mOsm urea (p) is hyper osmotic but isotonic. why?

- Because the only solution to consider is the non penetrating solutes. seeing as the urea will have no problem moving in and out of the cell thus an equal exchange. But the 300 NaCl cannot penetrate the solutes thus needing to move the water from one side to another thus making the volume change.
- Only non penetrating solutes will give a change in confirmation (volume)

**Endocytosis and Exocytosis:**

- Substances can also enter and leave cells without crossing the plasma membrane via endocytosis and exocytosis, respectively
- Most endocytic vesicles fuse with endosomes, which may transfer vesicle contents for enzymatic breakdown in lysosomes, or recycle contents to plasma membrane
- Exocytosis provides a means of adding components to the plasma membrane and a route by which membrane impermeable molecules (ex.proteins) can be released into the extracellular space
- Certain pathogens can use endocytic machinery to gain entry into, and infect cells
- Alternative functions of endocytosis :
  - Transcellular transport
  - Eadosomal processing
  - Recycling the membrane
  - Destroying engulfed materials

**Epithelial Transport:**

- Epithelial cells line hollow organs or tubes and regulate the absorption or secretion of substances across these surfaces.

- Two way for substances to cross the epithelial layer
  - By diffusion between adjacent cells - the **paracellular** pathway - limited by **tight junctions**
  - Diffusion into and out of epithelial cells- **the transcellular pathway**
- The **luminal (apical)** membrane or **serosal (basolateral)** membranes contains different channels and transporters which allows substances to undergo a net movement from a [low] on one side of the epithelium to a [higher] on the other side.

**Transepithelial Transport of Solutes:**

- Transepithelial transport of most organic solutes involves their movement by secondary active transport driven by the downhill floe of sodium ions

**Water follows by osmosis:**

- The active transport of sodium through an epithelium increases the osmolarity on one side of the cell and decreases it on the other, causing water to move by osmosis in the same direction as the transported sodium.