SODIUM BALANCE – Overview

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How are solute and solvent related to solution?

- **Solution** is made up of **Solute** and **Solvent**,
- **Concentration** of solution is a ratio of two variables:
  - Amount of Solvent (**Water**),
  - Amount of Solute (e.g., **Na^+** ions),
- **Molar concentration = Amount of Solute in 1000ml of solution,**
- Molar concentration is represented as **[ ],**
- Concentration of solution can change when either or both variables change For example:
  - Solution containing **[Na^+]** of 140mmol/L may become 130mmol/L if amount of **Na^+** ions in solution is reduced or amount of Solvent (water) is increased;

What are the electrolytes (Solutes) in ECF and ICF?

- Na^+ is Principal Cation in ECF,
- K^+ is Principal Cation in ICF,
- Proteins and Phosphates are the main Anions in ICF,
- Cl^- ions & HCO_3^- ions are main Anions in ECF,
- Na^+ is highest in ECF; it contributes to plasma Osmolality,
- Urea & Creatinine are measured with plasma electrolytes because they provide an indication of Renal Function,
- Increase in plasma [Urea] and [Creatinine] indicates decrease in Glomerular Filtration Rate in the kidneys;

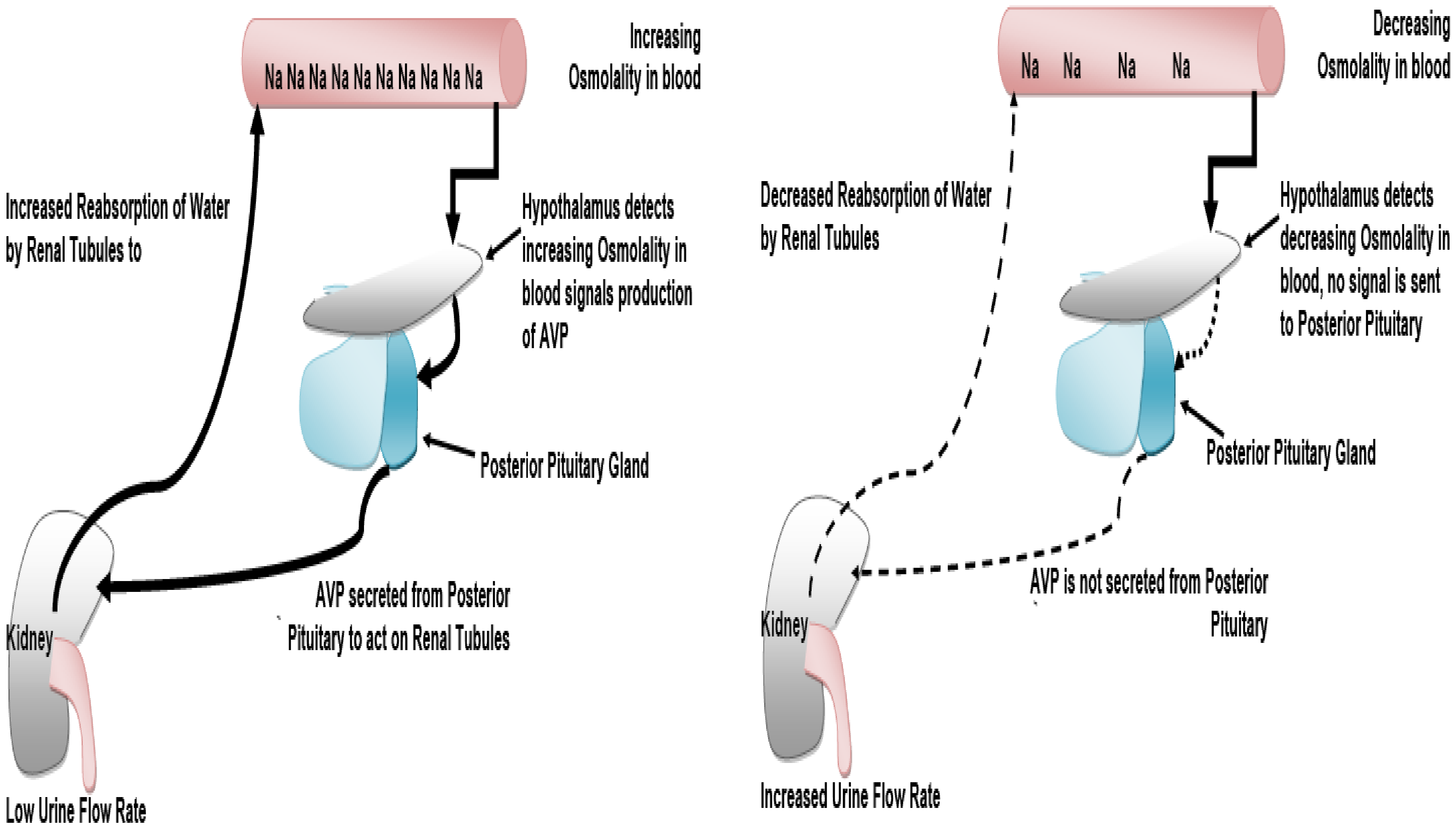
- **How are the Solvent (Water) and Solutes regulated?**

How is water (solvent) balance regulated?

- Water balance is regulated by Arginine Vasopressin (AVP)
- AVP: hormone produced by Posterior Pituitary Gland;
- AVP tightly regulates water excretion by kidneys;
- Osmolality in ICF is equal to that in ECF;
- Specialized cells in Hypothalamus maintain Osmolality between ICF and ECF;
- When Hypothalamus detects differences in Osmolality between ICF and ECF it regulates secretion of AVP;

- Regulation is as follows:
  - **Rising Osmolality promotes secretion of AVP,**
  - **Declining Osmolality switches off secretion of AVP,**
  - **AVP causes water to be retained by the kidneys,**
- Fluid deprivation results in stimulation of AVP secretion causing reduction in Urine Flow Rate to about 0.5 ml/min to conserve body water;
- Within ONE hour after drinking about 2 liters of water, Urine Flow Rate may rise to about 15 ml/min as AVP secretion is Shut Down;
- By regulating water Excretion or Retention, AVP maintains normal concentrations of Electrolytes within the body (**Figs. 1a & 1b**)

Figs. 1a & 1b: Regulation of water balance by AVP: Increased Osmolality activates AVP secretion and reduces urine flow rate; Decreased Osmolality inhibits secretion of AVP and increases urine flow rate;



SODIUM BALANCE

- **Amount consumed should equal amount loss per day;**
- Total Sodium in body is made up of:
  - Non-Exchangeable Sodium = 25% of Total Sodium;
  - Exchangeable sodium = 75% of Total Sodium;
- Non-Exchangeable Sodium is in Bone and Cartilage and has slow turnover rate;
- Most Exchangeable Sodium is in ECF;
- Exchangeable Sodium circulates in Plasma as Na^+;
- Normal range of Na^+ in plasma = 135 to 145mmol/L;
- Plasma [Na^+] does not indicate Sodium balance;
- Plasma [Na^+] primarily reflects body water content;

Sodium intake and Sodium loss:

Sodium Intake:

- By individuals vary, depending on Habits, Taste, Availability;
- Health individuals: Total body sodium does not change even if intake falls to 5mmol/day or increases to 750mmol/day;

Sodium Loss:

- Loss of sodium varies among individuals;
- Sodium is excreted **mainly** via the Kidneys;
- Some is lost in sweat (5 mmol/day) and feces (5 mmol/day);
- GIT is major route of pathological Sodium loss;
- **Diarrhea** and **Vomiting** may result in death from Salt loss and Water Depletion in **Pediatric Cases**;

What factors regulate Sodium excretion?

- Sodium Excretion is regulated by:
  - Intrinsic Renal Mechanisms,
  - Level of Aldosterone Secretion,
  - Secretion of Atrial Natriuretic Factor (ANF),

What is the role of Aldosterone in regulation of Sodium Balance?

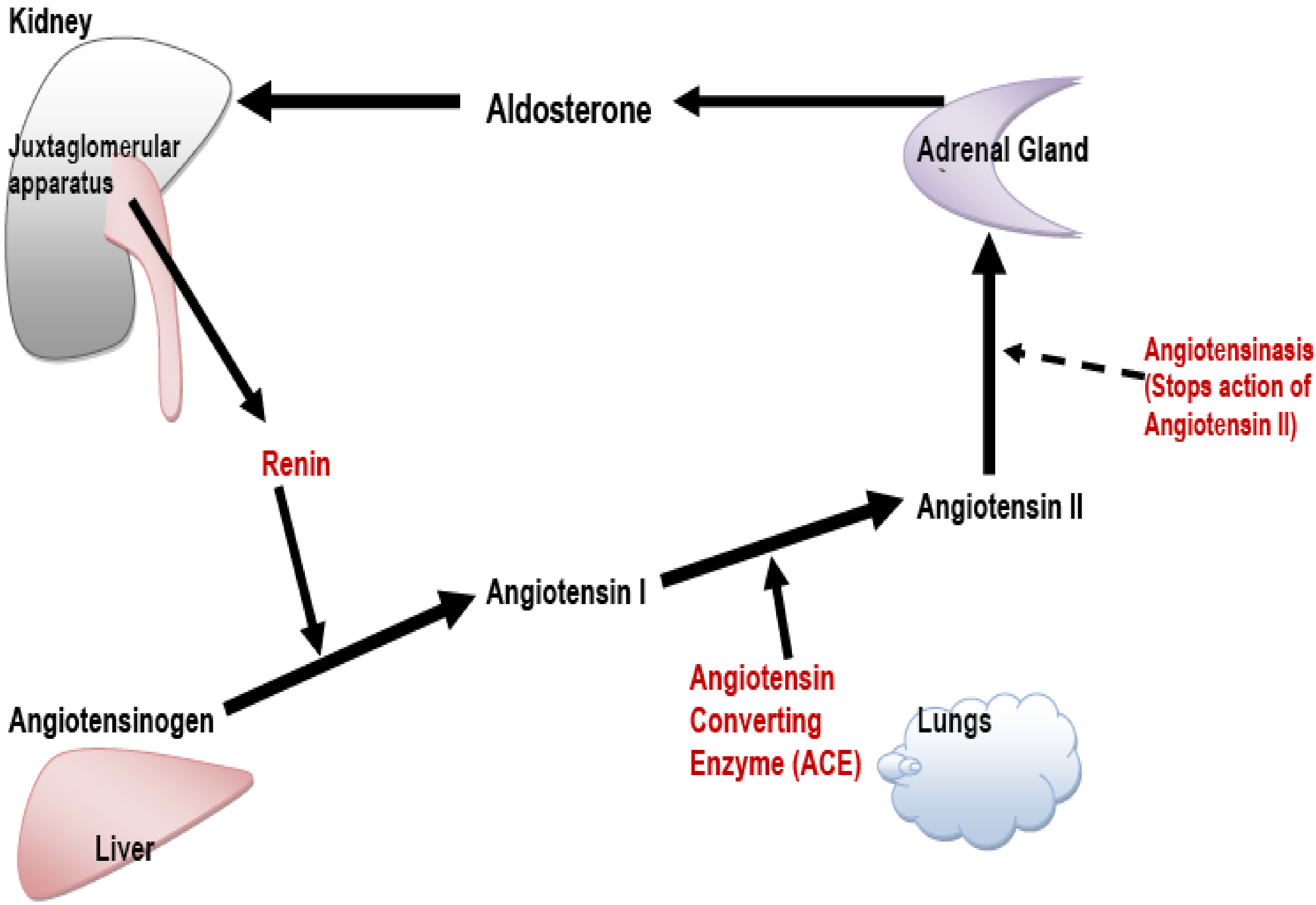
- Aldosterone is a hormone produce in Adrenal Cortex;
- **Aldosterone:**
  - Decreases Urinary Sodium Excretion by Increasing the Re-absorption of Na^+ in Renal Tubules in exchange for Tubule excretion of K^+ and H^+ ,
  - Decreases loss of **Na^+** in Sweat Glands and Mucosal Cells of the Colon, but in normal circumstances these effects are minimal;

How is secretion of Aldosterone regulated?

- Major stimulus for secretion of Aldosterone:
  - Volume of ECF, and Osmolality of ECF,
- Specialized cells in Juxtaglomerular Apparatus of the Kidneys detect decrease in Blood Pressure and secrete **Renin**,
- Renin converts **Angiotensinogen** to **Angiotensin I**;
- **Angiotensin Converting Enzyme** (ACP) in Lungs converts **Angiotensin I** to **Angiotensin II**;
- **Angiotensin II** acts on Adrenal Cortex to produce **Aldosterone**
- Aldosterone acts on Kidney Tubules causing reabsorption of **Na^+** in exchange for excretion of **K^+, and H^+ (Fig. 2)**

- Action of Angiotensin II is terminated by **Angiotensinasis**;

Fig. 2: Regulation of Sodium balance by Aldosterone?



What is the role of Atrial Natriuretic Factor (ANF) in regulation of Sodium balance?

- Atrial Natriuretic Factor (ANF) is a polypeptide hormone secreted by Cardiocytes in the Right Atrium of the Heart – thus, it is a Cardiac Hormone;
- ANF increases Urinary Sodium excretion: **Natriuresis;**
- ANF regulates ECF volume,
- ANF regulates concentration of Sodium in plasma,

What is Osmolality (Osmolarity)?

- Osmolality: concentration of **osmotically active** particles in solution,
  - particles that cannot cross semi-permeable membrane,
- Water moves across cell membrane separating ECF from ICF;
- Osmosis is flow of solvent across semi-permeable membrane from low solute concentration to higher solute concentration,
- Osmotic pressure: driving force for water to change the concentration of osmotically active particles,
- Osmolality of ICF = Osmolality of ECF: Isotonic solutions,
- Water moves across cell membrane to maintain Osmolality of ECF & ICF; even if the cells shrink or expand in volume,

How is Osmolality of Serum or Plasma calculated?

- Osmotically active solutes are used:
- Simple formula for calculating Osmolality :

$$\textbf{Serum Osmolality} = 2[Na^+]$$

  - (Unit is **mmol/kg,** or **mOsmol/Kg** or **mOsmol/L**; Unit for Plasma or Serum Sodium ion is **mmol/L**);

- Simple formula is used only when Plasma [**Urea]** and [**Glucose]** are within the reference ranges;
- **NB**: Normal Osmolality of Serum or Plasma (other body fluids except urine) is **285 to 295 mmol/kg** (**285 to 295 mOsmol/L**);

Example for calculating Osmolality

Normal Conditions (Plasma or Serum [Urea] and [Glucose] are within normal range)

- ECF Osmolality can be roughly estimated as:

→ $$P_{osm} = 2 \cdot [Na]_p = 270 - 290 \text{ mOsm}$$

{Where P_{osm} is plasma Osmolality;. Since intracellular Osmolarity is the same as extra-cellular Osmolality under normal conditions, this also provides an estimate of intracellular Osmolality}

Example for calculation of Osmolality

Clinical Laboratory Measurement:

- Plasma Osmolarity measured in Clinical laboratory also includes [Glucose] and [Urea];
- Normally the contribution from Glucose and Urea is small
- Under certain Pathological conditions, the concentrations of these substances can be very high;
- Plasma Osmolality measured in clinical laboratory:

$$\mathbf{P = 2[Na^+] + 2[K^+] + [Glucose] + [Urea]}$$

(**P** = Plasma or Serum Osmolality)

- Glucose and BUN normally contribute about 5mOsm each (about 2%) of Plasma Osmolarity measured in the clinical lab

How is effective Osmole different from ineffective Osmole?

- **Ineffective Osmole:**
  - Urea crosses the semi-permeable cell membranes just as easily as water, therefore it does not contribute to redistribution of water between ECF and ICF;
- **Effective Osmoles:**
  - Glucose, Na^+ and Anions associated with Na^+ do not cross the semi-permeable membrane;
  - They have concentration gradients across the cell membrane and are osmotically active;
  - They determine the distribution of water between ECF and ICF;

How is Effective Osmole calculated?

Two ways for calculating Effective Osmole:

- Effective Osmole:

$$P\ (\text{effective}) = 2[Na^+] + [\text{Glucose}]$$

- Effective Osmole:

$$P\ (\text{effective}) = P\ (\text{measured}) - [\text{Urea}]$$

- (**P** = plasma or serum Osmolality)

What is Osmolal Gap and how is it calculated?

OSMOLAL GAP (OG):

- Difference between **Measured Osmolality (MO)** and **Calculated Osmolality (CO)**

Osmolal Gap (OG) = MO – CO

- Large positive OG helps to identify presence in serum of osmotically active substances, e.g, Ethanol, Methanol, Iso-propanol, Ethylene Glycol and Acetone,
- Proper interpretation of OG also requires knowledge of **Anion Gap (AG)**, and blood pH

$$\textbf{Anion Gap} = [Na^+] - \{[HCO_3^-] + [Cl^-]\}$$

What is HYPONATRAEMIA?

- **Hyponatraemia:** significant fall in [Na^+] below the reference range for plasma or serum;
  - (what is the reference range for Serum [Na^+] in PMGH?)

- **"Hypo-Osmolality"** is synonymous with **Hyponatraemia**

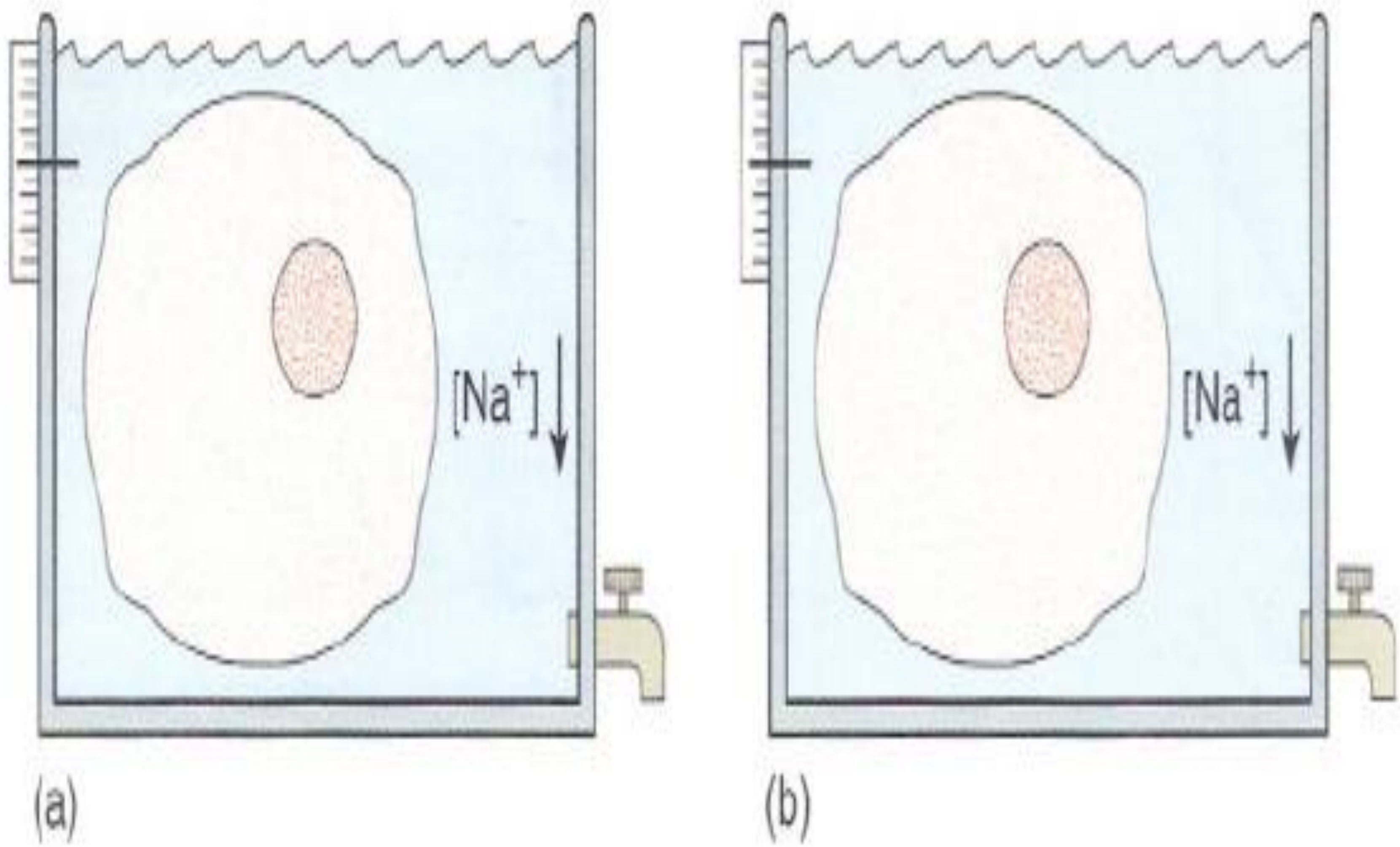
because **Na^+** is major cation in ECF in sufficient amount such that a decrease in concentration would significantly affect the Osmolality;

List two possibilities of Hyponatraemia?

- Hyponatraemia due to Fluid **Retention:**
  - More fluid than normal is retained in the body compartments and dilutes the constituents in ECF causing **Hyponatraemia**; (**Fig. 3a**)

- Hyponatraemia due to **Loss of Na^+ ions :**
  - When loss of **Na^+** ions exceeds loss of fluid, Hyponatraemia may result, (**Fig. 3b**)
  - Example: Loss of fluid (vomiting or fistulae) that contain **Na^+ ions** are replaced simply by water;

Fig. 3a: Fluid retention in ECF & ICF causing Hyponatraemia
Fig. 3b: Sodium loss resulting in Hyponatraemia [Gwa et al 1999]

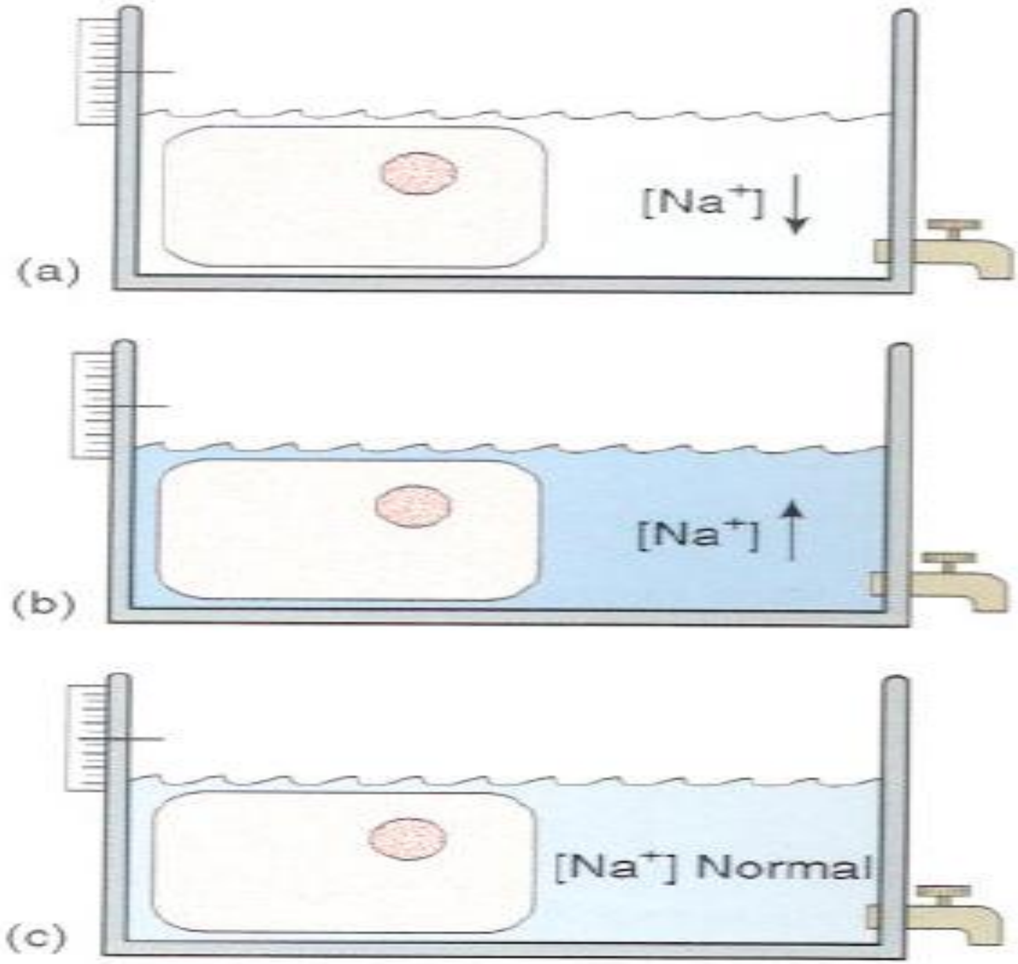


- Water tank model in **Fig. 3a & 3b** emphasizes that Biochemical observation of Hyponatraemia gives no clear explanation about the Volume of the ECF compartment;
- Both laboratory results of these patients indicate Hyponatraemia, with no indication of fluid retention or loss of Sodium;
- **Thus, the courses of Hyponatraemia should be made by proper History taking and Clinical Examination of the Patient, not by assessing the laboratory results alone;**

- Some patients with reduced ECF volume may present with either **Reduced**, **Increased** or **Normal** Plasma Sodium concentration (**Figure 4a, 4b, 4c**),

- **These diagrams clearly indicates that Clinicians MUST always give greater emphasis and attention to History, Signs and Symptoms of the Patients not to Laboratory results on plasma Sodium alone;**

Fig. 4a: Reduced ECF with Hyponatraemia (low plasma Sodium conc.);
Fig. 4b: Reduced ECF with Hypernatraemia (high plasma Sodium conc.);
Fig. 4c: Reduced ECF with Normal plasma Sodium conc. (Gwa et al 1999)



What are some causes of Hyponatraemia with fluid retention?

- Decreased water excretion: Examples:
  - Nephrotic Syndrome,
  - Renal Failure;
- Increased Water Intake: Examples:
  - Inappropriate IV Saline,
  - Compulsive water drinking,

TAKE NOTE:

- If fluid loss is not apparent from the Clinical history of a patient then the reason for the Hyponatraemia is usually WATER RETENTION;
- Hyponatraemia due to water overload without decrease in total body Sodium is the commonest Biochemical disturbance encountered in clinical practice;
- Further consideration of Hyponatraemia of this type, depends on whether the patient has **Edema**:
- Two possible conditions are:
  - **Edematous Hyponatraemia,**
  - **Non-Edematous Hyponatraemia,**

EDEMATOUS HYPONATRAEMIA

- Patients with generalized Edema have an increase in both Total Body Sodium and Water:
- Some causes of Edema:
- **Heart Failure:**
  - Effective blood volume may be reduced because pumping action of the heart is unable to maintain a satisfactory circulation of Blood and ECF;
- **Hypo-albuminaemia**,
  - Effective blood volume is reduced because Hypo-albuminaemia lowers Plasma Oncotic Pressure, which disrupts normal exchange of solutes and fluid in capillary bed reducing circulation of Blood and ECF;
  - Edema occurs if albumin concentration falls very low;

- In response to reduced effective blood volume, **Aldosterone** is secreted and causes Sodium retention to allow the ECF volume to expand;

- Reduction in effective blood volume is one of the Non-Osmotic Stimuli for the secretion of AVP and consequently water is retained;

- **Hyponatraemia results from the Retention of relatively more water than Sodium in the ECF;**

What are some causes of Hypo-albuminaemia?

- **Decreased biosynthesis** of albumin due to:
  - Liver disease;
  - Loss of albumin exceeds biosynthetic capacity of liver as occurs in Nephrotic syndrome;
  - Malnutrition or Mal-absorption;
- **Abnormal distribution or dilution:**
  - Over-hydration or if there is increased capillary permeability as occurs in Septicemia;
- **Abnormal excretion or degradation:**
  - Nephrotic Syndrome, Protein-losing Enteropathies, Burns, Haemorrhage and Catabolic states;

NON-EDEMATOUS HYPONATRAEMIA

- Patients with Non-Edematous Hyponatraemia have normal total body Sodium and exhibit the features of **Syndrome of Inappropriate Anti-diuresis (SIAD**)
- Patients are Hyponatraemic, Normotensive, have normal Glomerular Filtration Rate (GFR) and normal serum Urea and Creatinine concentrations;
- Urine Flow Rate is usually less than 1.5 liter/day;

- SIAD may occur in conditions such as:
  - Infections, e.g. Pneumonia,
  - Malignancy, e.g. Carcinoma of Bowel or Lung,
  - Trauma, e.g. Abdominal Surgery,
  - Drug-induced, e.g. Thiazide Diuretics, Chlorpropamide
    - Patients suffering from any of the above may have Non-Osmotic AVP stimulation and, if they are exposed to excessive water loads, in the form of oral drinks or intravenous glucose solutions, they will become Hyponatraemic;

HYPONATRAEMIA DUE TO SODIUM LOSS

- Occurs during Pathological Sodium Loss
- May be from GIT or Urine
- Vomiting (severe and protracted as occurs in Pyloric Stenosis)
- Diarrhoea;
- Fistula

Urinary loss of Sodium may be due to

- Aldosterone deficiency due to failure of the Adrenal Glands (Addison's disease);
- Drugs that antagonize Aldosterone action;
- Initially in such patients:
  - Sodium loss is accompanied by Water loss and Serum Sodium ion concentration remains normal;
  - As Sodium loss proceeds, the reduction in ECF and blood volume stimulates AVP secretion;
  - Non-osmotic control of AVP secretion overrides osmotic control mechanism;
  - Increased AVP secretion causes water retention and thus the patient becomes Hyponatraemic;
  - Patient becomes Hyponatraemic because a deficit of Isotonic Sodium-containing fluid is replaced only by water, either Orally or Intravenously;
- In all cases patients should be given Oral Rehydration Solution,

REFERENCES

1. A. Gwa, RA Cowan, DJ O'Reilly, MJ Stewart, J Shepherd. "An illustrated colour text: Clinical Biochemistry" 2nd Edition, 1999, Churchill Livingstone, London.
2. G Beckett, S. Walker, P. Rae, P. Ashby. "Lecture Notes: Clinical Biochemistry" 7th Edition, 2008, Blackwell Publishing, Australia.
3. VJ. Temple. "Biochemistry 1001: Review and Viva Voce Questions and Answers Approach", Sterling Publishers Private Ltd 2012, New Delhi.

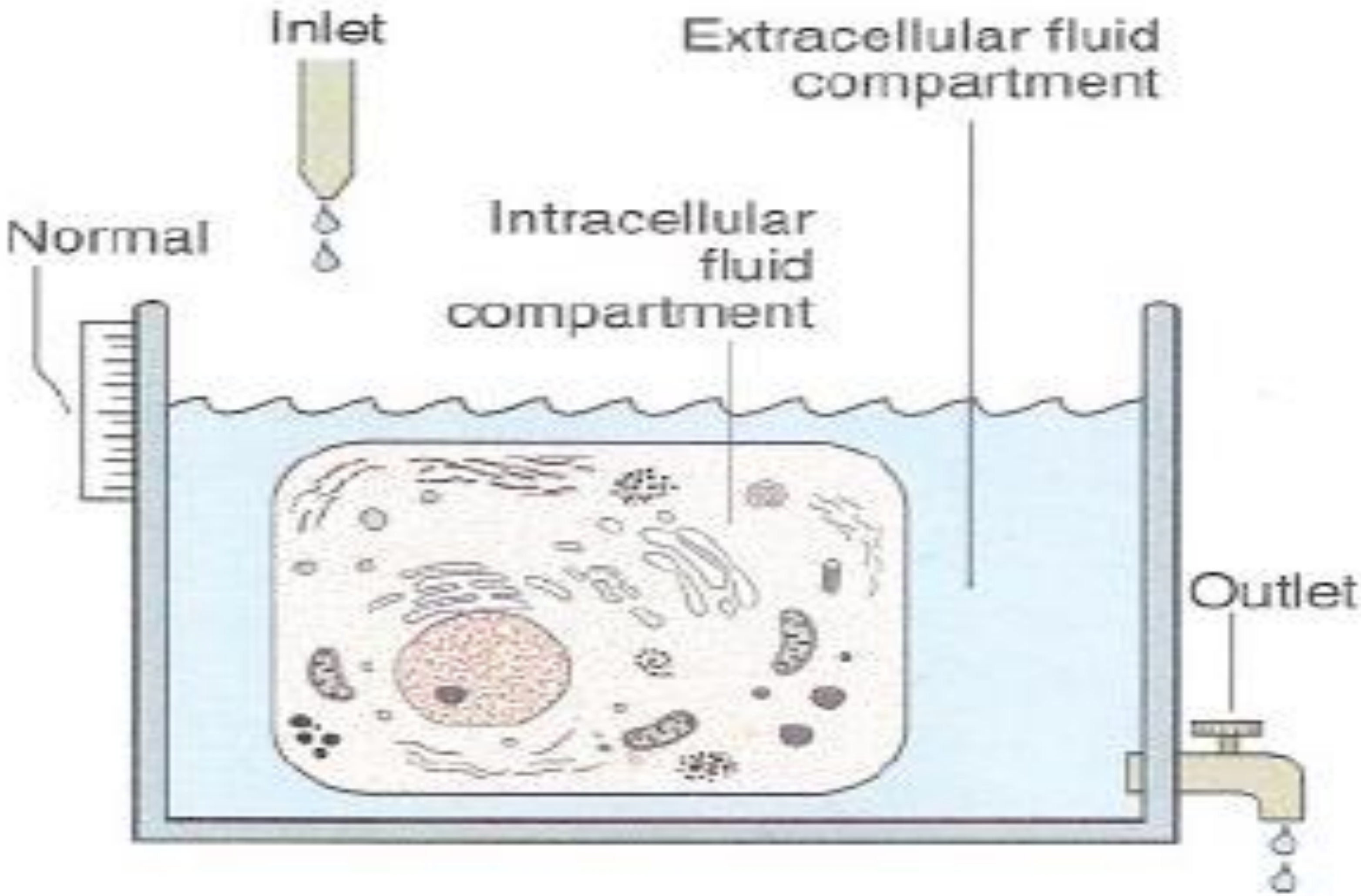
WATER (FLUID) BALANCE (STEADY STATE)

- Amount of daily water intake varies among individuals ;
- Amount of daily water loss varies among individuals;
- Water loss is normally seen as changes in volume of urine production;
  - Urine Flow Rate can vary widely in a very short time;
- **To maintain water balance**:
  - Amount of daily water intake must equal amount of daily water loss,
- Disruption of balance may cause:
  - Net water gain: Over hydration; or
  - Net water loss: Dehydration

How much fluid (water) is contained in the body?

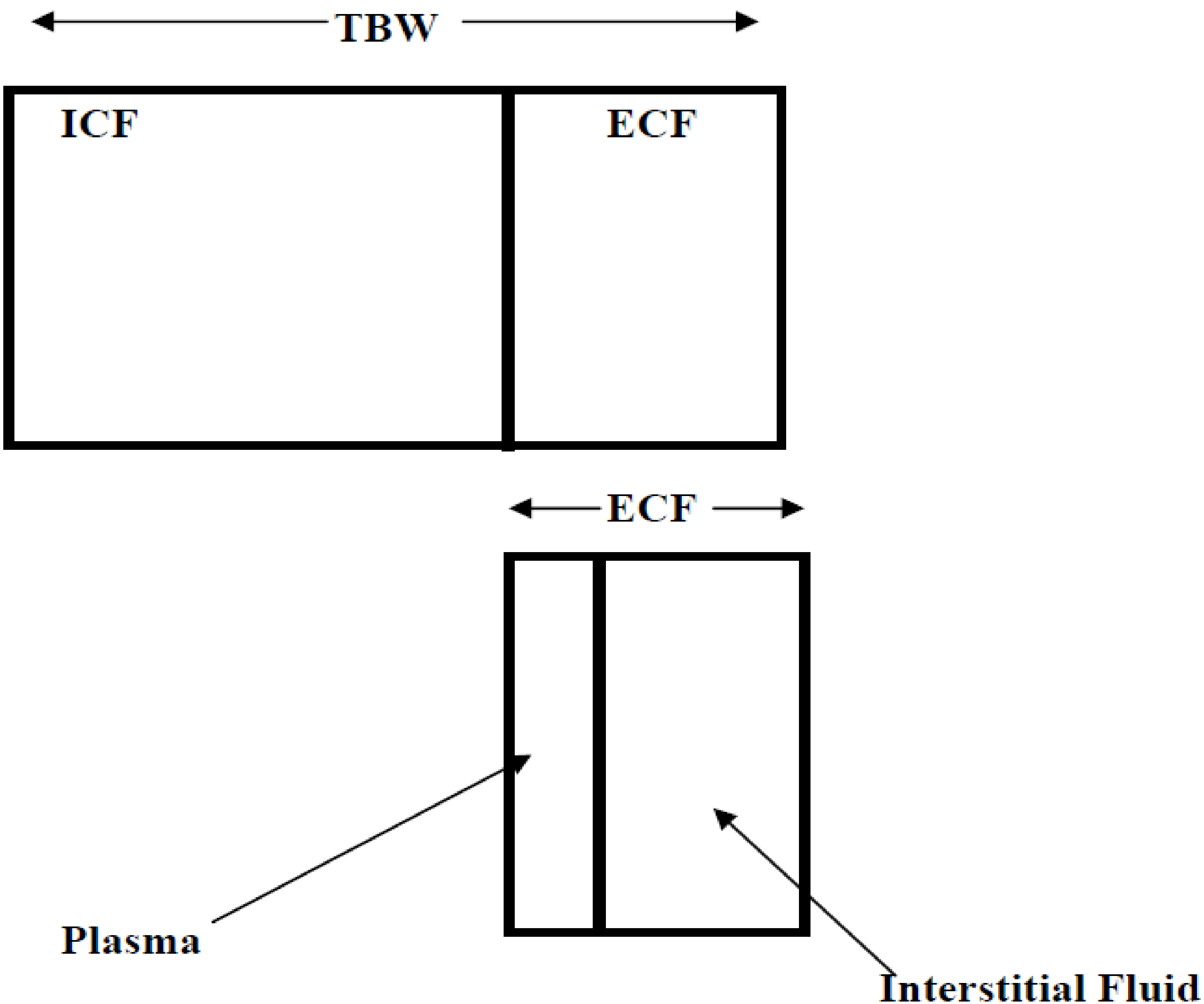
- Water/Fluid is a major body constituent;
- Average person (70 kg) contains about 42 liters of Total Body Water (TBW);
- TBW is about 60% of total body weight;
- TBW separated into 2 major compartments;
  - Extra-Cellular Fluid Compartment (ECF),
  - Intra-Cellular Fluid Compartment (ICF),
    - **Fig. 1**: Water tank model illustration ECF, ICF, TBW,

Fig. 1: Schematic diagram of water tank model to illustrate body fluid compartments [Gwa et al 1999]



What are the major fluid compartments in the body?

- Major fluid compartments **(Fig. 2)**:
  - Intra-Cellular Fluid Compartment (**ICF**): Volume of Fluid Inside Cells;
    - **ICF constitute about 66.6% of TBW,**
  - Extra-Cellular Fluid Compartment (**ECF**): Volume of Fluid Outside Cells;
    - **ECF constitute about 33.3% of TBW,**
- ECF made up of **Plasma** and **Interstitial Fluid**
  - Plasma: about 25% of ECF,
  - Interstitial Fluid: about 75% of ECF,


TBW
ICF
ECF
ECF
Plasma
Interstitial Fluid

What are the major sources and routes of fluid intake?

- Some major sources of fluid intake:
  - Water Drinking;
  - Water contained in various foodstuffs;
  - Metabolic water;

What are some major routes in the body for fluid loss?

- Some major routes of fluid loss:
- Urinary loss,
- Fecal loss
- Insensible water loss: evaporation from Respiratory Tract and Skin Surface (sweat is sensible since it has a purpose);

- Sweat Losses:
  - Room temperature: sweating is 25% of H_2O loss;
  - Cold environments: H_2O loss in sweat decreases;
  - Warm environments, exercise: sweat losses increases;
- Pathological losses: vascular bleeding, vomiting, and diarrhea;

What are some consequences of fluid loss?

- Selective loss of fluid from ICF or ECF gives rise to distinct signs and symptoms:
  - Loss of ICF can cause Cellular Dysfunction: leads to Lethargy, Confusion and Coma;
  - Loss of ECF: leads to Circulatory Collapse, Shock, Renal shutdown;
  - Loss of TBW: similar effects as loss of ICF or ECF;
- Signs of (substantial) fluid loss is spread across ICF & ECF;

How is the state of hydration of a patient assessed?

- State of Hydration indicates volume depletion or Volume expansion of body fluid compartments;
- It is assessed Clinically by appropriate Clinical signs;
- It involves:
    - History taking to identify water intake and water loss;
    - Signs and Symptoms indicating,
        - Dehydration (loss of fluid),
        - Over-hydration (accumulation of fluid)
- **Figs 3a & 3b:** illustrate effect of Volume Depletion and Volume Expansion on water thank model of body fluid compartments,

Fig. 3a: Dehydration: Loss of fluid in ICF & ECF due to increased urinary output; Fig. 3b: Overhydration: Increased fluid intake resulting in increased fluid volume in ICF and ECF [Gwa et al 1999]