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Body Fluid

Body Water

Amount of wtaer present in the body is called body water. It is 40 litres in a man of 70kg, averaging 57% of total body wt in adult male and 51% in an adult female and it may be as high as 75% of the total body wt.

Role of body water *(Funetion)*

1. It is an essential constituent of all cells of the body and the milieu interior (ECF).
2. It serves as a transport medium by which nutrient pass into cells and excretory products come out.
3. Most of the cellular reactions occur in the body in this fluid medium.
4. It is a valuable solvent in which various substances such as electrolytes, nonelectrolytes, enzymes, hormones, vitamins, even fat soluble compounds are carried from one place to another.
5. It plays a vital role in maintenance of body heat.
6. It is helpful in maintaining the form and texture of the tissue.

Daily intake of body water (in ml/day)

	Normal	*Prolonged heavy exercise*
Fluids ingested	2100	?
From metabolism (oxidation of carbohydrate)	200	200
Total intake	*2300*	*?*

(Ref. Guyton & Hall-11th Edition, Page-292)

Daily loss (output) of body water (in ml/day)

	Normal	*Prolonged heavy exercise*
Insensible - Skin	350	350
Insensible - Lungs	350	650
Sweat	100	*5000*
Feces	100	100
Urine	1400	*500*
Total output	*2300*	*6600*

(*N.B. Insensible water loss :* We are not conciously aware of it, even though it occurs in all living humans.)

(Ref. Guyton & Hall-11th Edition, Page-292)

Water balance

The balance between water intake and water output of the body is called water balance.

Classification of water balance

Water balance are of two types :

a. Positive water balance
b. Negative water balance.

Positive water balance : When the water intake exceeds the output that means water is retained in the body is called positive water balance.

It occurs in the following conditions :

i. During growing period.
ii. Recovery from a disease.
iii. During pregnancy.
iv. Changes of dietary habits i.e. from high fatty acid to high protein diet.

Negative water balance : When water output exceeds the water intake, it is called negative water balance.

It occurs in the following conditions :

i. Vomittig, diarrhoea and haemorrhage.
ii. Burns.
iii. Excessive salivation like peptic ulcer, creatinism.
iv. When intake of fluid is restricted e.g starvation, narvosa, anorexia.
v. Unconscious state e.g. cerebrovascular accident.
vi. Addision's diseases, diabeties, hypofunction of adrenal gland.

Regulation of water balance

Water balance of the body are controlled by the following factors :

1. *Thirst mechanism :* Slight fall in blood volume or ECF volume causes osmosis of water out of the neural cells of the thirst center, thus shrinking the cell, causes drinking to maintain water balance. Intracellular dehydration, dryness of mouth cavity also stimulate thirst center thus increases water intake.
2. *Condition of kidney :* Kidney is the main regulator of the homeostasis of body fluid. According to situation and by excreting either dilute or concentrated urine kidney maintain water balance.
3. *Temperature and humidity :* Rise of temperature and

humidity incerases loss of water through the skin and respiratory tract. The thermoregulatory mechanism helps to steady the temperature and so indirectly maintain water balance.

4. *Endocrine glands :*
   i. Adrenal gland : It secretes aldosterone that by regulating the salt absorption from kidney also helps to maintain water balance.
   ii. ADH of posterior pituitary plays an important role in water balance by maintaining the reabsorption of water from kidney.
5. *Hypothalamus :* Supraoptic nuclei of anterior hypothalamus contain osmoreceptors. When osmolarity in the ECF rises, water pulls out of the osmoreecptors causing them to shrink and increasing their rate of discharge and maintain water balance through ADH.

Factors affecting water balance

1. Thirst mechanism
2. Condition of kidney
3. Temperature & humidity
4. Endocrine glands
5. Hypothalamus
6. Electrolyte and water balance
7. Diet.

Body Fluid

Water of the body together with its dissolved solute is called body fluid. It plays an important role in the basic physiology of body function. Most of the cellular reaction occurs in the fluid media. Water is the essential constituents of the body fluid and constitute about 57% of body weight in 70 kg adult male and 51% in adult female. In new born it is about 75%.

Types of body Fluid

1. *Intracellular fluid (ICF) :* The fluid inside the cells of the body is known as intracellular fluid. It constitutes about 40% of total body weight.
   The total amount of ICF = 28 liters.
2. *Extra cellurlar fluid (ECF) :* The fluid in the spaces out side the cells of the body known as extracellular fluid. It includes both the interstitial fluid that circulates in the spaces between the cells and also fluid of the blood plasma. It constitutes about 20% of total body weight.
   The total amount of ECF = 14 liters.

Body fluid compartments

The body fluid is mainly distributed between two compartments

1. *Intracellular fluid compartment :* It is the sumtotal of the fluid content of all cells of the body. It is about 28 liters.
2. *Extracellular fluid compartment :* It is the fluid out side of the cell. It is about 14 litres.
   The extracellular fluid in turn is divided into the *interstitial fluid* and blood *plasma.*
3. There is another small compartment of fluid that is referred to as ***transcellular fluid.*** It is usually considered to be a specialized type of extracellular fluid, although in some cases, its composition may differ markedly from that of plasma or interstitial fluid. It constitutes about 1 to 2 liters.This compartments includes fluids-
   i. Synovial fluid
   ii. Peritonial fluid
   iii. Pericardial fluid
   iv. Intraocular fluid
   v. Cerebrospinal fluid.

(Ref. Guyton & Hall-11th Edition, Page-292)

% of total body fluid compartments

Total body water (42 litre or) 60%

a. *Intracellular component* of body water (28 litres or) 40%

b. *Extracellualr component* of body water (14 litres) 20%

i. 25% of the extracellular component is in the vascular system-(*plasma*-3 litres) 5%

ii. 75% of the extracellular component is in the outside of blood vessels (*Interstitial fluid*) 15%

(Total blood volume is about 8% of body weight.)

(Ref. Ganong 22th Edition; Page-01)

iii. *Transcellular fluid : 1 to 2 litres*
(This compartment includies- fluid in the synovial, peritonial, pericardial, and intraoccular spaces, as well as the cerebrospinal fluid).

N.B. In the average 70-kilogram adult human, the total body water is about 60% of the body weight, or about 42 liters. This percentage can change, depending on age, sex, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associaed with an increased percentage of the body weight that is fat, which in turn decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight. Therefore when discussing the *average body fluid* compartments, we should realize that variations exits, depending on age, sex, and percentage of body fat.

(Ref. Guyton & Hall-11th Edition, Page-293)

ECF is more important than ICF- Explain

ECF is called "internal enviornment of the body" and it is more important than that of ICF. Because its constituents are accurately regulated so that the cells remain bathed continually in a fluid containing the proper electrolytes and nutrients for continued cellular function.

Important constituent of extracellular fluid :

Extracellular fluid, including the plasma and the interstitial fluid, contains large amounts of sodium and chloride ions, reasonably large amounts of bicarbonate ions, but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions.

The composition of extracellular fluid is carefully regulated by various mechanisms but especially by the kidneys. This allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

Ionic composition of plasma and interstitial fluids are : Because the plasma and interstitial fluids are separated only by highly permeable capillary membranes, their ionic compositions are similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; the capillaries have a low permeability to the plasma proteins and, therefore, leak only small amounts of proteins into the interstitial spaces in most tissues.

Because of the Donnan effect, the concentration of positively charged ions (cations) is slightly greater (about 2 per cent) in the plasma than in the interstitial fluid; this effect is the following: the plasma proteins have a net negative charge and, therefore, tend to bind cations, such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins. Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid, compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions. For practical purposes, however, the concentrations of ions in the interstitial fluid and plasma are considered to be equal.

(Ref. Guyton & Hall-11th Edition, Page-293)

Important constituents of the intracellular fluid :

The intracellular fluid is separated from the extracellular fluid by a selective cell membrane that is highly permeable to water but not to most of the electrolytes in the body.

In contrast to the extracelluiar fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and *almost no calcium ions*. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein, almost four times as much as in the plasma. *(Ref. Guyton & Hall-11th Edition, Page-293)*

Difference between ECF and ICF

ECF	*ICF*
1. ECF contains large amount of sodium, chloride and bicarbonate ions plus nutrients for the cells such as oxygen, glucose, aminoacids and fatty acids.	1. ICF contain large amount of potassium, magnesium & phosphate ions.
2. It is needed for the maintenance of cellular function and called the internal environment of the body or milieu interior.	2. It is not called so.
3. Small amount of protein present in the the ECF.	3. Large amount of protein in ICF.

Osmolar substances in plasma extracellular fluid (ECF) and intracellular fluid (ICF)

	Plasma (mosm/liter of H_2O)	*Interstitial (mosm/liter of H_2O)*	*Intracellular (mosm/liter of H_2O)*
Na^+	*142*	139	14
K^+	4.2	4	*140*
Ca^{++}	1.3	1.2	0.001
Mg^{++}	0.8	0.7	20
Cl^-	*108*	108	4
HCO_3^-	24	28.3	10
HPO_4^- /$H_2PO_4^-$	2	2	*11*
SO_4^-	0.5	0.5	1
Phosphocreatine	-	-	45
Carnosine	-	-	14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate	-	-	5
Hexose monophosphate	-	-	3.7
Glucose	5.6	5.6	-
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/liter	301.8	300.8	301.2
Corrected osmolar activity (mOsm/liter)	282.0	281.0	281.0

Total osmotic pressure at 37°C (mm Hg)	*5443*	*5423*	*5423*

(Ref. Guyton & Hall-11th Edition, Page-294)

Principle for measuring body fluid

The volume of any fluid compartment of the body can be measured by placing a substance in the compartment, allowing it to disperse evenly throughout the fluid, and then measuring the extent to which the substance become diluted. Then a sample of the dispersed fluid is removed and the concentration of the substance is analyzed. The volume of the fluid compartment can then measured from the following formula :

$$\text{Volume} = \frac{\text{Quantity of the test substancce instilled}}{\text{Concentration per ml of dispersed fluid}}$$

$$= \frac{\text{Volume x concentration of the test substancce injected}}{\text{Concentration per ml of dispersed fluid}}$$

This method can be used to measure the volume of virtually any compartment in the body as long as- *i. the indicator disperses evenly throughout the compartment, ii. the indicator disperses only in the compartment that is being measured, and iii. the indicator is not metabolized or excreted.* Several substances can be used to measure the volume of each of the different body fluids.

Determination of volumes of specific body fluid compartments

Measurement of body fluid volumes :

Volume	*Indicators*
Total body water	$^{3}H_20$, $^{2}H_20$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as Total body water- ECF)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as Blood volume = plasma volume/(1 - hematocrit)
Interstitial fluid	(Calculated as ECF - Plasma volume)

(Ref. Guyton & Hall-11th Edition, Page-296)

Measurement of total body water

Indicators : Radioactive water (tritium, $^{3}H_20$) or heavy water (deuterium, $^{2}H_2O$) and antipyrine can be used to measure total body water. Antipyrine, which is very lipid soluble and can rapidly penetrate cell membranes and distribute itself uniformly throughout the intracellular and extracellular compartments.

Procedure : Radioactive water (tritium, $^{3}H_20$) or heavy water (deuterium, $^{2}H_2O$) mix with the total body water within a few hours after being injected into the blood, and the dilution principle can be used to calculate total body water.

Total body water-

$$= \frac{\text{Volume x concentration of the test substancce injected}}{\text{Concentration per ml of dispersed fluid}}$$

(Ref. Guyton & Hall-11th Edition, Page-295)

Example : Suppose 100 ml of D_2O in isotonic saline is injected intravenously to a man of weighting about 70 kg. After an equilibirium of 2 hours, the plasma samples is analysed and D_2O concentration is found to be 0.0023 mosm/liter. During the period of equilibrium it is found to have a loss of average 0.5% of the quantitity adminstered. So, the volume of the distribution will be-

$$= \frac{\text{Quantity administered - Quantity excreted}}{\text{Equilibrium concentration}}$$

$$= \frac{100 - 0.5}{0.0023}$$

$$= \frac{99.5}{0.0023}$$

= 43260 ml

= 43.26 liter.

Measurement of extracellular fluid volume

Indicators : The volume of extracellular fluid can be estimated using any of several substances that disperse in the plasma and interstitial fluid but do not readily permeate the cell membrane. They include radioactive sodium, radioactive chloride, radioactive iothalamate, thiosulfate ion, and inulin.

Procedure : When any one of these substances (indicators) is injected into the blood, it usually disperses almost completely throughout the extracellular fluids within 30 to 60 minutes and the dilution principle can be used to calculate the extracellular fluid volume.

Extracellular fluid volume -

$$= \frac{\text{Volume x concentration of the indicator injected}}{\text{Concentration per ml of dispersed fluid}}$$

Some of these substances, however, such as radioactive sodium, may diffuse into the cell in small amounts. Therefore, one frequently speaks of the *sodium space*, or the *inulin space* instead of calling the measurement the true extracellular volume.

(N.B. Short notes on Na- Space)

(Ref. Guyton & Hall-11th Edition, Page-296)

Calculation of intracellular volume

The intracellular volume cannot he measured directly. However, it can be calculated as-

inward through the capillary membrane when pif is positive but outward when pif is negative.

True Interstitial fluid pressure :

In loose subcutanous tissue is = -3 mm Hg.

In tightly encased tissue i.e the pressure under- neath with tight fibrous fascial coverings are always more positive.

The plasma colloidal osmotic pressure : Which tends to cause osmosis of fluid inward through the membrane. It is about 28 mm of Hg.

The interstitial fluid colloidal osmotic pressure : Which tends to cause osmosis of fluid outward through the membrane. It is about 8 mm of Hg.

(Ref. Guyton & Hall-11th Edition, Page 185)

Forces causing filtration at the arterial end of the capillary

The approximate average forces operating at the arterial end of the capillary that cause movement through the capillary membrane are

a. *Forces tending to move fluid outward :*
   i. Capillary hydrostatic pressure 30 mm of Hg.
   ii. Negative interstitial free fluid pressure (-)3mm Hg *(i.e. Outward force 3 mm of Hg).*
   iii. Interstitial fluid colloidal osmotic pressure 8 mm Hg.

   Total outward force = 41 mm Hg. (30 + 3 + 8 =41 mm Hg).

b. *Forces tending to move fluid inward :*
   i. Plasma colloidal osmotic pressure 28 mm Hg.

   Total inward force = 28 mm Hg.

Summation of forces :

i. Out ward forces = 41 mm Hg
ii. In ward forces = 28 mm Hg.

Net out ward force = 13 mm Hg (41 - 28 = 13 mm of Hg).

This 13 mm Hg filtration pressure causes on the average about 0.5 percent of the plasma to filter out of the arterial end of the capillaries into the interstitial spaces.

(Ref. Guyton & Hall-11th Edition, Page 189)

Force causing reabsorption of fluid at the venous end of the capillary

The low pressure at the venous end of the capillary changes the balance of forces infavour of absorption as follows :

a. *Forces tending to move fluid inward :*
   i. Plasma colloidal osmotic pressure 28 mm Hg.
   Total inward force = 28 mm of Hg.

b. *Forces tending to move fluid outward :*
   i. Capillary pressure : 10 mm of Hg.
   ii. Negative interstitial free fluid pressure : (-)3 mm of Hg (i.e Outward force 3 mm of Hg).
   iii. Interstital fluid colloid osmotic pressure : 8 mm Hg.

   Total outward force : 21 mm of Hg (10+3+8 mm Hg)

Summation of forces :

i. Inward force : 28 mm Hg.
ii. Outward force : 21 mm Hg.

Net inward force = 7 mm of Hg (28 - 21 = 7 mm of Hg).

Thus the force that causes fluid to move into the capillary, 28 mm of Hg, is greater than that opposing reabsorption, 21 mm Hg. The difference, 7 mm of Hg is the reabsorption pressure. This reabsorption pressure. (7 mm Hg) draws the fluid from the tissue space into the venous end of the capillary.

(Ref. Guyton & Hall-11th Edition, Page 189)

Factors responsible for fluid exchange between the blood capillaries and intestitial space

The exchanges of fluid between plasma and the tissue spaces (interstitial spaces), both ways is a continuous process. The exchange has been considered to be due to the operation of the following factors :

1. *Capillary membrane and its permeability :*
   a. Lipid soluble materials through the cells
   b Lipid insoluble materials through the pores.
   c. Large molecular substances like protein dextran etc. through pinocytosis.
2. Diffusion
3. Filtration
4. Absorption
5. Metabolic activity of the tissue.

Interstitium and interstitial fluid

About one sixth of the body consists of spaces between cells, which collectively are called the *interstitium.* The fluid in these spaces is the *interstitial fluid.*

a. *Structure of the interstitium* : It has two major types of solid structures :
   i. *Collagen fiber bundles* : The collagen fiber bundles extend long distances in the interstitium.

   Function : They are extremely strong and therefore provide most of the tensional strength of the tissues.
   ii. *Proteoglycan filaments* : The proteoglycan filaments, however, are extremely thin, coiled molecules composed of about 98 per cent hyaluronic acid and 2 per cent *protein.* These molecules are so thin that they can never be seen with a light microscope and are difficult to demonstrate even with the electron microscope. Nevertheless, they form a mat of very fine reticular filaments aptly described as a *brush pile.*

Intracellular volume = Total body water - Extracellular volume.

(Ref. Guyton & Hall-11th Edition, Page-296)

Measurement of Plasma volume

Indicators Used : Plasma volume can be measured by using indicators are-

1. Evans blue dye (also called, T-1824)
2. Serum albumin labelled with radio-active iodine (^{125}I-albumin).

(Ref. Guyton & Hall-11th Edition, Page-296)

Procedure : Suppose 10 ml of venous blood of a subject is taken in a heparinized tube. This serves as the control sample. 5 ml of a 5% solution of Even's blue (T-1824) in diluted water is then injected intravenously. 10 minute after the injection another 10 ml of sample is withdrawn from the vein into another heparinized tube. The haematocrit of both sample are determined. The optical density of the dye stained plasma is estimated. 0.01 ml of the dye is then diluted to 5 ml (dilution is 1 : 500) with the control plasma and its optical density is measured.

So plasma volume (ml)

= Dye solution injected x dye Solution stadarisation

$$\times \frac{\text{Density of standard}}{\text{Density of unknown}}$$

Calculation of interstitial fluid volume

Interstitial fluid volume cannot be measured directly but it can be calculated as-

Interstitial fluid volume = Extracellular fluid volume - Plasma volume

Measurement of blood volume

The avreage blood volume of a normal adult man is approximately 5,000 ml. On the average approximtely 3000 ml of this is plasma and remainder 2000 ml is blood cells.

Here plasma volume is obtained same as ECF.

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

For example, if plasma volume is 3 liters and hematocrit is 0.40, then total blood volume would be calculated as

$$\text{Total blood volume} = \frac{3}{1 - 0.40}$$

$$= 5 \text{ liters}$$

Another way to measure blood volume is to inject into the circulation red blood cells that have been labeled with radioactive material. After these mix in the circulation, the radioactivity of the mixed blood sample can be measured, and the total blood volume can be calculated using the dilution principle. A substance frequently used to label the red blood cells is radio-active chromium (^{51}Cr), which binds tightly with the red blood cells.

(Ref. Guyton & Hall-11th Edition, Page-296)

Criteria of indicator used for measuring body fluid :

1. The indicator must mix with the volume of fluid within reasonable time.
2. It is not changed in anyway in the body.
3. It must be non-toxic.
4. It should be excreted in the urine within reasonable period.

Criteria of indicator used for measuring body water :

i. It must not be toxic.

ii. It is distributed through out the body water compartments and then diffuses readily across the cell membrane.

Q. 00. *Why Evan's blue and radioactive substances are choosen for plasma volume measurement?*

Ans. It is used because it is :

i. Must not be toxic

ii. Must not alter plasma volume

iii. Must not easily pass into tissue or be excreted

iv. Must not be taken up by the phagocytic cell of the blood.

Lean body mass

Lean body mass is that mass of the body which can be determined by substrating the fat content of body from the total body weight.

Lean body mass = total body weight - its fat content.

Measurment of lean body mass : Lean body mass can be calculated from the specific gravity of the subject determined by weighting the subject in air divided by the weight of displaced water.

Effective Filtration Pressure

It is the net filtration pressure that operating the filtration at the arterial or venous end.

Factors affecting the effective filtration pressure :

It depends upon :

i. Capillary pressure.

ii. Interstitial fluid pressure.

iii. Plasma colloidal osmotic pressure.

iv. Interstitial fluid colloidal osmotic pressure.

The capillary pressure (p_c) : Which tends to force fluid outward through the capillary membrane. It is averaging about 17 mm of Hg *(Indirect functional measurement, Direct cannulation of the capillaries averaging about 25 mm of Hg).*

The interstitial fluid pressure (p_f) : Which tends to force fluid

b. ***Gel in the interstitium*** : The fluid in the interstitium is derived by filtration and diffusion from the capillaries. It contains almost the same constituents as plasma except for much lower concentrations of proteins because proteins do not pass outward through the pores of the capillaries with ease. The interstitial fluid is entrapped mainly in the minute spaces among the proteoglycan filaments. This combination of the proteoglycan filaments and the fluid entrapped within them has the characteristics of a *gel* and therefore is called *tissue gel.*

Because of the large number of proteoglycan filaments, it is difficult for fluid to flaw easily through the tissue gel. Instead, it mainly diffuses through the gel; that is, it moves molecule by molecule from one place to another by kinetic motion rather than by large numbers of molecules moving together.

Diffusion through the gel occurs about 95 to 99 per cent as rapidly as it does through free fluid. For the short distances between the capillaries and the tissue cells, this diffusion allows rapid transport through the interstitium not only of water molecules but also of electrolytes, small molecular weight nutrients, cellular excreta, oxygen, carbon dioxide, and so forth.

(Q. What is the importance of the proteoglycan in preventing rapid flow of fluid in the tissue spaces?)

c. ***Free fluid in the interstitium*** : Although almost all the fluid in the interstitium normally is entrapped within the tissue gel, occasionally small *rivulets of free fluid* and *small free fluid vesicles* are also present, which means fluid that is free of the proteoglycan molecules and therefore can flow freely. When a dye is injected into the circulating blood, it often can be seen to flow through the interstitium in the small rivulets, usually coursing along the surfaces of collagen fibers or surfaces of cells. The amount of *free fluid* present in *normal* tissues is slight, usually much less than 1 per cent. Conversely, when the tissues develop edema, these small pockets and rivulets of free fluid expand tremendously until one half or more of the edema fluid becomes freely flowing fluid independent of the proteoglycan filaments.

(Ref. Guyton & Hall-11th Edition; page 184)

Function of the interstitial fluid

1. It constitute the internal medium in which the tissue cells are bathed. The cells draw O_2 and nutrition from the tissue fluid and excrete their metabolites into it. Hence, tissue fluid may be regraded as the medium which supplies all the immediate requirements of the cells.
2. It acts as a great reservior of water, salts, nutrition etc.
3. It maintain the turgescence of the connective tissue and the skin.
4. The tissue fluid in some cases afford protection and maintain shape of the structure.

Quantity of plasma that filters out of the capillary

0.5 percent of the plasma fluid that filters out of the arterial ends of the capillaries flow through the tissue spaces to the venous ends of the capillaries, where 9/10th flows into the lymphatic capillaries.

(Ref. Guyton & Hall-11th Edition)

Volumes and osmolalities of extracellular & intracellular fluid in abnormal states

Some of the different factors that can cause extracellular and intracellular volumes to change markedly are-

1. Ingestion of water
2. Dehydration
3. Intravenous infusions of different types of solutions.
4. Loss of large amounts of fluid from the gastrointestinal tract.
5. Loss of abnormal amounts of fluid by sweating or through the kidneys.

One can calculate both the changes in intracellular and extracellular fluid volumes and the types of therapy that should be instituted if the following basic principles are kept in mind :

1. *Water moves rapidly across cell membranes*; therefore, the osmolarities of intracellular and extracellular fluids remain almost exactly equal to each other except for a few minutes after a change in one of the compartments.
2. *Cell membranes are almost completely impermeable to many solutes*; therefore, the number of osmoles in the extracellular or intracellular fluid remains constant unless solutes are added to or lost from the extracellular compartment.

With these basic principles in mind, we can analyze The effects of different abnormal fluid conditions on extracellular and intracellular fluid volumes and osmolarities.

(Ref. Guyton & Hall-11th Edition, Page 299)

Saline solution

Effect of adding saline solution to the extacellular fluid : If an *isotonic saline solution* is added to the extracellular fluid compartment, the osmolarity of the extracellular fluid does not change; therefore, no osmosis occurs through the cell membranes. The *only effect is an increase in extracellular fluid volume*. The sodium and chloride largely remain in the extracellular fluid because the cell membrane behaves as though it were virtually impermeable to the sodium chloride.

If a *hypertonic solution* is added to the extracellular fluid, the extracellular osmolarity increases and causes osmosis of water out of the cells into the extracellular compartment. Again, almost all the added sodium chloride remains in the extracellular compartment, and fluid diffuses from the cells into the extracellular space to achieve osmotic equilibrium. *The net effect is an increase in extracellular volume (greater*

than the volume of fluid added), a decrease in intracellular volume, and a rise in osmolarity in both compartments.

If a *hypotonic solution* is added to the extracellular fluid, the osmolarity of the extracelluiar fluid decreases and some of the extracellular water diffuses into the cells until the intracellular and extracellular compartments have the same osmolarity (Figure 25-6C): *Both the intracellular and the extracellular volumes are increased by addition of hypotonic fluid, although the intracellular volume increases to a greater extent.*

(Ref. Guyton & Hall-11th Edition, Page 299)

Calculation of fluid shifts and osmolarities after infusion of hypertonic saline : We can calculate the sequential effects of infusing different solutions on extracellular and intracellular fluid volumes and osmolarities. ***For example***, *if we infuse 2 liters of a hypertonic 2.9 per cent sodium chloride solution into the extracellular fluid compartment of a 70-kilogram patient whose initial plasma osmolarity is 280 mOsm/L*, what would be the intracellular and extracellular fluid volumes and osmolarities after osmotic equilibrium?

1. The *first step* is to calculate the initial conditions, including the volumes, concentrations, and total milliosmoles in each compartment. Assuming that extracellular fluid volume is 20 per cent of body weight and intracellular fluid volume is 40 per cent of body weight. the following volumes and concentrations can he calculated.

Step 1. Initial conditions :

	Volumes (Liters)	*Concentration (mOsml/L)*	*Total (mOsm)*
Extracellular fluid	14	280	3920
Intracellur fluid	28	280	7840
Total body fluid	42	280	11,760

Next, *we calculate the total milliosmoles added to the extracellular fluid in 2 liters of 2.9 per cent sodium chloride*. A 2.9 per cent solution means that there are 2.9 g/100 ml, or 29 grams of sodium chloride per liter. Because the molecular weight of sōdium chloride is about 58 g/mol, this means that there is about 0.5 mole of sodium chloride per liter of solution. For 2 liters of solution, this would be 1 mole of sodium chloride. Because 1 mole of sodium chloride is about equal to 2 osmoles (sodium chloride has two osmotically active particles per mole), *the net effect of adding 2 liters of this solution is to add 2000 milliosmoles of sodium chloride to the extracellular fluid.*

2. In *Step 2, we calculate the instantaneous effect of adding 2000 milliosmoles of sodium chloride to the extracellular fluid along with 2 liters of volume* : Instantineously, there would be no change in the *intracellular fluid* concentration or volume, and there would be no osmotic equilibrium. In the *extracellular fluid*, however, there would be an additional 2000 milliosmoles of total solute, yielding a total of 5920 milliosmoles. Because the extracellular compartment now has 16 liters of volume, the concentration can be calculated by dividing 5920 milliosmoles by 16 liters to yield a concentration of 370 rnOsmol/L. Thus, the following values would occur instantly after adding the solution.

Step 2. Instantaneous effect of adding 2 liters of 2.9 per cent sodium chloride :

	Volumes (Liters)	*Concentration (mOsml/L)*	*Total (mOsm)*
Extracellular fluid	16	370	5920
Intracellur fluid	28	280	7840
Total body fluid	44	No equilibrium	13,760

3. In the *third step*, we *calculate the volumes and concentrations that would occur within a few minutes after osmotic equilibriurn develops* : In this case, the concentration is in the intracellular and extracellular fluid compartments would be equal and can be calculated by dividing the total milliosmoles in the body, 13,760, by the total volume, which is now 44 liters. This yields a concentration of 312.7 mOsm/L. Therefore, all the body fluid compartments will have this same concentration after osmotic equilibrium. Assuming that no solute or water has been lost from the body and that there is no movement of sodium chloride into or out of the cells, *we then calculate the volumes of the intracellular and extracellular compartments* : the *intracellular fluid volume* is calculated by dividing the total milliosmoles in the intracellular fluid (7840) by the concentration (312.7 mOsm/L) to yield a volume of 25.1 liters. *Extracellular fluid volume* is calculated by dividing the total milliosmoles in extracellular fluid (5920) by the concentration (312.7 mOsm/L) to yield a volume of 18.9 liters. Again, these calculations are based on the assumption that the sodium chloride added to the extracellular fluid remains there and does not move into the cells.

Step 3. Effect of adding 2 liters of 2.9 per cent sodium chloride after osmotic equilibrium :

	Volumes (Liters)	*Concentration (mOsml/L)*	*Total (mOsm)*
Extracellular fluid	18.9	312.7	5920
Intracellur fluid	25.1	312.7	7840
Total body fluid	44.0	312.7	13,760

Thus, one can see from this example that adding 2 liters of a hypertonic sodium chloride solution causes a 4.9 liter increase in extracellular fluid volume while decreasing intracellular fluid volume by 2.9 liters.

This method of calculating changes in intracellular and extracellular fluid volumes and osmolarities can be applied to virtually any clinical problem of fluid volume regulation. An understanding of the mathematical aspects of osmotic equilibria between intracellular and extracellular fluid compartments is essential for understanding almost all fluid abnormalities of the body and their treatment.

(Ref. Guyton & Hall-11th Edition, Page 299, 300)

Glucose and other solutions administered for nutritive purposes :

Many types of solumions are administered intravenously to provide nutrition to people who cannot otherwise take adequate amounts of nutrition. *Glucose solutions* are widely used, and *amino acid* and *homogenized fat solutions* are used to a lesser extent. When These solutions are administered, their concentrations of osmotically active substances are usually adjusted nearly to isotonicity or they are given slowly enough that they do not upset the osmotic equilibria of the body fluids. After the glucose or other nutrients are metabolized, an excess of water often remains, especially if additional fluid is ingested. Ordinarily, the kidneys excrete this in the form of a very dilute urine. The net resull is, therefore, addition only of the nutrients to the body.

(Ref. Guyton & Hall-11th Edition, Page 301)

Clinical abnormalities of fluid volume regulation : Hyponatremia and Hypernatremia

The primary measurement that is readily available to the clinician in evaluating a patient's fluid status often is the plasma sodium concentration. Plasma osmolarity is not routinely measured but because sodium and its associated anions (mainly chloride) account for more than 90 per cent of the solute in the extracellular fluid, plasma sodiurn concentration is a reasonable indicator of plasma osmolarity under many conditions.

When plasma sodium concentration is reduced below normal (about 142 mEq/L), a person is said to have *hyponatrernia.*

When plasma sodium concentration is elevated above normal, a person is said to have *hypernatremia.*

(Ref. Guyton & Hall-11th Edition, Page 301)

Causes of hyponatremia : Excess water or loss of sodium.

Decreased plasma sodium concentration can result from loss of sodium chloride from the extracellular fluid or addition of excess water to the extracellular fluid. A primary loss of sodium chloride usually results in *hypo-osmotic dehydration* and is associated with decreased extracellular fluid volume. Conditions that can cause *hyponatremia owing to loss of sodium chloride include diarrhea and vomiting. Overuse of diuretics* that inhibit the ability of the kidneys to conserve sodium and *certain types of sodium-wasting kidney diseases* can also cause modest degrees of hyponatremia. Finally, *Addison's disease*, which results from decreased secretion of the hormone aldosterone, impairs the ability of the kidneys to reabsorb sodium and can cause a modest degree of hyponatremia.

Hyponatremia can also be *associated with excess water retention*, which dilutes the sodium in the extracellular fluid, a condition that is referred to as *hypo-osmotic overhydration*. For example, excessive secretion of antidiuretic hormone, which causes the kidney tubules to reabsorb more water, can lead to hyponatremia and overhydration.

(Ref. Guyton & Hall-11th Edition, Page 301)

Causes of hypernatremia : Water loss or excess sodium.

Increased plasma sodium concentration, which also causes increased osmolarity, can be due either to loss of water from the extracellular fluid, which concentrates the sodium ions, or to an excess of sodium in the extracellular fluid. When there is primary loss of water from the extracellular fluid, this results in *hyperosmotic dehydration*. This condition can occur from an inability to secrete antidiuretic hormone, which is needed for the kidneys to conserve water. As a result of lack of antidiuretic hormone, the kidneys excrete large amounts of dilute urine (a disorder referred to as diabetes insipidus), causing dehydration and increased concentration of sodium chloride in the extracellular fluid. In certain types of renal diseases, the kidneys cannot respond to antidiuretic hormone, also causing a type of *nephrogenic diabetes insipidus*. A more common cause of hypernatremia associated with decreased extracellular fluid volume is dehydration caused by a water intake that is less than the water lost from the body, as can occur with sweating during heavy exercise.

Hypernatremia can also occur as a result of excessive sodium chloride added to the extracellular fluid. This often result in *hyperosmotie overhydration* because excess extracellular sodium chloride is usually associated with at least some degree of water retention by the kidneys as well. For example, excessive secretion of the sodium-retaining hormone aldosterone can cause a mild degree of hypernatremia and overhydration. The reason that the hypernatremia is not more severe is that increased aldosterone secretion causes the kidneys to reabsorb greater amounts of water as well as sodium.

N.B. Thus, in analyzing abnormalities of plasma sodium concentration and deciding on proper therapy, one should first determine whether the abnormality is caused by a primary loss or gain of sodium or a primary loss or gain of water.

(Ref. Guyton & Hall-11th Edition, Page 302)

Extracellular volume depletion

Deficiency of H_2O and Na^+ causes shrinkase both of the interstitial space and of the blood volume. A simple water

deficit reduces the ECF and ICF proportionately. A NaCl deficit always decreases the ECF volume.

a. *Isosmotic volume depletion* : Only ECF volume decrease with no changes in osmolality. This is due to :
   i. Haemorrhage
   ii. Gastrointestinal fluid loss
      - vomiting
      - diarrhoea.
   iii. Fluid loss in burn.

ii. *Hyperosmotic volume depletion* : Both the ECF and ICF volume decrease with increased osmolality of both compartments. Common causes are:
   a. Inadequate intake
   b. Diabetes insipidus
   c. Diabetes mellitus
   d. Excessive sweating
   e. Fever.

iii. *Hyposmotic volume depletion* : It is characterized by decrease in ECF volume (ICF volume increases in this case) with decrease osmolality of both ECF and ICF compartment. *Causes are* :
   a. Renal loss of NaCI
   b. Addison's disease (decrease circulating aldosterone)

Effects of extraeellular volume depletion (dehydration)

Effects of extracellular volume depletion (i.e dehydration) are :

1. Increase thirst
2. Muscle cramps
3. Nausia and vomitting
4. Cold extremities (due to peripheral vasoconstriction)
5. Tachycardia
6. Loss of skin elasticity
7. Postural hypotension
8. Low jugular venous pressure
9. Arterial hypotension (a late sign).

Principle of management of extraeellular volume depletion

The overridden principle of treatment is aim to replace what is missing :

i. Hemorrhage : replace whole blood
ii. Loss of plasma : treat with human plasma or plasma substitute
iii. Loss of water and electrolytes : treat by replacement with water and electrolytes (as in vomiting and diarrhoea)

ORS

ORS is oral rehydreation solution.

i. *Composition of ORS* : The world health organization (WHO) oral rehydration solution is :
   a. Sodium : 90 mmol/litre
   b. Potassium : 20 mmol/litre
   c. Chloride : 80 mmol/litre
   d. Citrate : 10 mmol/litre
   e. Glucose : 111 mmol/litre.

ii. The presence of glucose in the ORS has been shown to promote electrolyte absorption

iii. *Indication* : Correction of mild to moderate dehydration.

Hypovolaemia

Physiological response to hypovolaemia : Hypovolaemia means decrease effective circulatory volume. Hypovolaemia may results from both the exogenous volume losses (i.e. haemorrhage, burn) and endogenous losses (i.e sepsis, anaphylaxis). Hypovolaemia cause shrinkage both of the interstitial space and of the blood volume and have profound effects on organ function. The physiological responses that become activated to counteract the hypovolaemie state and to maintain the normal homeostatic condition are :

i. *Sympatho-adrenal response to hypovolaemia* : Hypovolaeinia causes reduction in the effective circulatory volume that results in hypotension. Hypotension stimulates sympathetic nervous activity and increases release of catecholamines (i.e. epinephrine and norepinephrine) from the adrenal medulla which causes :
   a. Generalized vasoconstriction (except brain and heart)
   b. Increase myocardial contractility
   c. Increase heart rate.
   Vasoconstriction is more marked in the skin, where it accounts for the coolness and pallor.

ii. *Cardio-vascular response* : Hypovolaemia leads to decrease in circulatory volume and thus reduces venous return, cardiac output and blood pressure.
   In hypotension arterial baroreceptors are stressed to a lesser degree and sympathetic output is increased. The effect are :
   a. Reflex tachycardia
   b. Vasoconstriction → increased peripheral resistance
   c. Venous return improved → increase cardiac output
   d. Blood pressure rises to normal levels

iii. *Neuroendocrine response* : A 10%-20% decrease in blood volume will evoke ADH release. Other endocrine hormones released in response to hypovolaemia are :
   a. ADH : improves antidiuresis
   b. Cortisol : causes fluid retention
   c. Beta-endorphin : is responsible for some of the cardiovascular changes.

iv. *Renal response* : A low circulatory blood volume causes reduction in renal perfusion, which in turn stimulates the

juxtaglomerular apparatus to release renin and ultimately increases circulatory angiotensin II level. Angiotensin II stimulates secretion of aldosterone by the adrenal cortex which causes sodium and water retention from renal tubules. This helps to restore the circulatory volume.

Oedema

i. *Definition* : Oedema means accumulation of excess fluid in the tissue space (interstitial space).

ii. *Basic mechanism* : The basic mechanism for oedema formation is increased shift of salt and water into interstitium. This is result from:
   a. Increased ECF volume
   b. Decreased plasma colloid osmotic pressure
   c. Increased venous pressure
   d. Increased microcirculatory permeability.

   Peripheral oedema is caused by expansion of the extracellular volume by at least 2 liters (15%)

iii. *Types* :
   a. Oedema may be generalized or local.
   b. It may pitting (due to protein deficiency) and non-pitting in nature.

iv. *Causes of oedema are* :
   1. Conditions associated with generalized.oedema
      a. Cardiac failure
      b. Nephrotic syndrome
      c. Hepatic cirrhosis
      d. Protein losing enteropathy
      e. Thiamine deficiency
      f. Pregnancy
      g. Drugs : NSAIDs, nifedipine.
   2. Conditions associated with localized edema :
      a. Trauma
      b. Inflammation
      c. Thrombosis
      d. Prolong immobility.

Regulation of extracellular fluid composition & volume

Introduction : The major homeostatic mechanisms that operate, primarily through the kidneys and the lungs, to maintain the ***tonicity***, the ***volume***, and the ***specific ionic composition***, particularly the H^+ *concentration* of the ECF. The interstitial portion of this fluid is the fluid environment of the cells, and life depends upon the constancy of this 'internal sea".

(Ref. Ganong 22th Edition; Page-729)

Defense of tonicity

The defense of the tonicity of the ECF is primarily the function of the *vasopressin-secreting* and *thirst mechanisms*. The *total body osmolality is directly proportionate to the total body sodium plus the total body potassium divided by the total body water,* so that changes in the osmolality of the body fluids occur when there is a disproportion between the amount of these electrolytes and the amount of water ingested or lost from the body.

i. *When the effective osmotic pressure of the plasma rises-* vasopressin secretion is increased and the thirst mechanism is stimulated. Water is retained in the body, diluting the hypertonic plasma, and water intake is increased.

ii. *Conversely, when the plasma becomes hypotonic* - vasopressin secretion is decreased and 'solute-free water' (water in excess of solute) is excreted.

In this way, the tonicity of the body fluids is maintained within a narrow normal range. In health, plasma osmolality ranges from 280 to 295 mosml/kg of H_2O, with vasopressin secretion maximally inhibited at 285 mosm/kg and stimulated at higher values.

(Ref. Ganong 22th Edition; Page-729)

Defense of volume

The volume of the ECF is determined primarily by the total amount of osmotically active solute in the ECF. Since $Na^+$and $Cl^-$are by far the most abundant osmotically active solutes in ECF, and since changes in Cl^- are to a great extent secondary to changes in Na^+, the amount of Na^+ in the ECF is the most important determinant of ECF volume. Therefore, the mechanisms that control Na^+ balance are the major mechanisms defending ECF volume. There is, however, a volume control of water excretion as well; *a rise in ECF volume inhibits vasopressin secretion, and a decline in ECF volume produces an increase in the secretion of this hormone.* Volume stimuli override the osmotic regulation of vasopressin secretion. Angiotensin II stimulates aldosterone and vasopressin secretion. It also causes thirst and constricts blood vessels, which help to maintain blood pressure. Thus, angiotensin II plays a key role in the body's response to hypovolemia. In addition, expansion of the ECF volume increases the secretion of ANP and BNP by the heart, and this causes natriuresis and diuresis.

In disease states, loss of water from the body (dehydration) causes a moderate decrease in ECF volume, because water is lost from both the intracellular and extracellular fluid compartments; but loss of Na^+ in the *stools* (diarrhea), *urine* (severe acidosis, adrenal insufficiency), or *sweat* (heat prostration) decreases ECF volume markedly and eventually leads to shock. The immediate compensations in shock operate principally to maintain intravascular volume, but they also affect Na^+ balance. In adrenal insufficiency, the decline in ECF volume is due not only to loss of Na^+ in the urine but also to its movement into cells.

Because of the key position of Na^+ in volume homeostasis, it is

not surprising that more than one mechanism has evolved to control the excretion of this ion.

When ECF volume is decreased, blood pressure falls. Glomerular capillary pressure declines, and the GFR therefore falls, reducing the amount of Na filtered. Tubular reabsorption of Na^+ is increased, in part because the secretion of aldosterone is increased. Aldosterone secretion is controlled in part by a feedback system in which the change that initiates increased secretion is a decline in mean intravascular pressure. Other changes in Na^+ excretion occur too rapidly to be due solely to changes in aldosterone secretion. For example, rising from the supine to the standing position increases aldosterone secretion. However, Na^+ excretion is decreased within a few minutes. and this rapid change in Na^+ excretion occurs in adrenalectamized subjects. It is probably due to hemodynamic changes and possibly to decreased ANP secretion.

(*N.B. Regulation of Na^+*)

(Ref. Ganong 22th Edition; Page-729)

Nervous and hormonal factors increase the effective ness of renal-body fluid feedback control :

(Basic mechanism of controlling blood volume /control of extracellular fluid volume by the kidney) : The nervous and hormonal mechanisms usually act in concert with the pressure natriuresis and pressure diuresis mechanisms, making them more effective *in minimizing the changes in blood volume, extracellular fluid volume, and arterial pressure* that occur in response to day-to-day challenges. However, abnormalities of kidney function or of the various nervous and hormonal factors that influence the kidneys can lead to serious changes in blood pressure and body fluid volumes.

i. ***Sympathetic nervous system control of renal excretion*** : *The arterial baroreceptor and low-pressure stretch receptor reflexes :* Because the kidneys receive extensive sympathetic innervation, changes in sympathetic activity can alter renal sodium and water excretion as well as regulation of extracellular fluid volume under some conditions. *For example, when blood volume is reduced by hemorrhage-* the pressures in the pulmonary blood vessels and *other low-pressure regions of the thorax decrease, causing reflex activation of the sympathetic nervous system. This in turn increases renal sympathetic nerve activity, which has several effects to decrease sodium and water excretion- i. constriction of the renal arterioles, with resultant decreased GFR; ii. increased tubular reabsorption of salt and water; and iii. stimulation of renin release and increased angiotensin II and aldosterone formation, both of which further increase tubular reabsorption.* And if the reduction in blood volume is great enough to lower systemic arterial pressure, further activation of the sympathetic nervous system occurs because of decreased stretch of the arterial baroreceptors located in the carotid sinus and aortic arch.

All these reflexes together play an important role in the rapid restitution of blood volume that occurs in acute conditions such as hemorrhage. Also, reflex inhibition of renal sympathetic activity may contribute to the rapid elimination of excess fluid in the circulation that occurs after eating a meal that contains large amounts of salt and water.

(Ref.Guyton & Hall 11th Edition; Page 377)

ii. ***Role of Angiotensin II in controlling renaI excretion*** : One of the body's most powerful controllers of sodium excreion is angiotensin II. Changes in sodium and fluid intake are associated with reciprocal changes in angiotensin-II formation, and this in turn contributes greatly to the maintenance of body sodium and fluid balances. That is, when sodium intake is elevated above normal, renin secretion is decreased, causing decreased anglotensin II formation. Because angiotensin II has several important effects in increasing tubular reabsorption of sodium, a reduced level of angiotensit II decreases tubular reabsorption of sodium and water, thus increasing the kidneys' excretion of sodium and water. The net result is to minimize the rise in extracellulai fluid volume and arterial pressure that would otheryise occur when sodium intake increases.

Conversel., when sodium intake is reduced below normal, increased levels of angiotensin II cause sodium and water retention and oppose reductions in arterial blood pressure that would otherwise occur. Thus, changes in activity of the renin-angiotensin system act as a powerful amplifier of the pressure natriuresis mechanism for maintaining stable blood pressures and body fluid volume.

(Ref.Guyton & Hall 11th Edition; Page 377)

iii. ***Role of Aldosterone in controlling renal excretion*** : Aldosterone increases sodium reabsorption, *especially in the cortical collecting tubules.* The *increased sodium reabsorption is also associated with increased water reabsorption and potassium secretion.* Therefore, the net effect of aldosterone is to make the kidneys retain sodium and water but to increase potassium excretion in the urine.

The function of aldosterone in regulating sodium balance is closely related to that described for angiotensin II. That is, with reduction in sodium intake, the increased angiotensin II levels that occur stimulate aldosterone secretion, which in turn contributes to the reduction in urinary sodium excretion and, therefore, to the maintenance of sodium balance. Conversely, with high sodium intake, suppression of aldosterone formation decreases tubular reabsorption, allowing the kidneys to excrete larger amounts of sodium. Thus, changes in aldosterone formation also aid the pressure natriuresis mechanism in maintaining sodium balance during variauons in salt intake.

(Ref.Guyton & Hall 11th Edition; Page 378)

iv. ***Role of ADH in controlling renal water excretion*** : ADH plays an important role in allowing the kidneys to form a small volume of concentrated urine while excreting normal amounts of salt. This effect is especially important during water deprivation, which strongly elevates plasma levels of ADH that in turn increase water reabsorption by the kidneys and help to minimize the decreases in extracellular fluid volume and arterial pressure that would otherwise occur. Water deprivation for 24 to 48 hours normally causes only a small decrease in extracellular fluid volume and arterial pressure. However, if the effects of ADH are blocked with a drug that antagonizes the action of ADH to promote water reabsorption in the distal and collecting tubules, the same period of water deprivation causes a substantial fall in both extracellular fluid volume and arterial pressure.

Conversely, when there is excess extracellular volume, decreased ADH levels reduce reabsorption of water by the kidneys, thus helping to rid the body of the excess volume.

Excess ADH secretion usually causes only small increases in extracellular fluid volume but large decreases in sodium concentration.

(Ref.Guyton & Hall 11th Edition; Page 379)

v. ***Role of atrial natriuretic peptide in controlling renal excretion*** : Some researchers believe that several natriuretic hormones may also contribute to volume regulation. One of the most important of the natriuretic hormones is a peptide referred to as atrial natriuretic peptide (*ANP*), released by the cardiac atrial muscle fibers. The stimulus for release of this peptide appears to be overstretch of the atria, which can result from excess blood volume. *Once released by the cardiac atria, ANP enters the circulation and acts on the kidneys to cause small increases in GFR and decreases in sodium reabsorption by the collecting ducts. These combined actions of ANP lead to increased excretion of salt and water, which helps to compensate for the excess blood volume.*

(Ref.Guyton & Hall 11th Edition; Page 379)

N.B. ***Other hormones acting on Kidney***

Parathormone : It is secreted by the parathyroid gland.

i. It increases the renal tubular reabsorption of Ca^{++} ion.

ii. It increases the renal tubular secretion of pho phate.

Growth hormone : Secreted by the anterior pituitary. It acts upon kidney and caused the release of somatomedins from kidney. These somatomedins help in bone and cartilage growth.

Control of blood pressure by the kidney *(Renin angiotensin mechanism) :* Renin is synthesized and stored in an inactive form called prorenin in the juxtaglomerular cells of the kidneys. When the arterial pressure falls intrinsic reactions in the kidneys themselves cause many of these prorenin molecules to split and release renin. Most of the renin enters the blood.

Renin is an enzyme, not a vasoactive substance itself. It acts enzymatically on another plasma protein, a globulin called renin substrate (or angiotensinogen), to release a 10-amino acid peptide, angiotengin-I. The renin persist in the blood for 30 minutes to an hour and continues to cause formation of angiotensin-I during this entire time.

Within a few seconds after formation of the angiotensin-I, two additional amino acids are split from it to form the 8-amino acid peptide angiotensin-II, catalyzed by the converting enzyme, present in the endothelium of the lung vessels. However, it persists in the blood only for a minute or two because it is rapidly inactivated by multiple blood and tissue enzymes collectively called angiotensinase.

During its persistence in the blood, Angiotensin-II causes :

a. Intense vasoconstriction in the arterioles and, less extent in the vein.

b. Decrease the excretion of both salt and water, this increase the extracellular fluid volume.

Thus the blood pressure is increased.

(Ref. Guyton & Hall 11th Edition)

Defense of specific ionic composition

Special regulatory mechanisms maintain the levels of certain specific ions in the ECF as well as the levels of glucose and other nonionized substances important in metabolism. The feedback of Ca^{2+}on the parathyroids and the calcitonin-secreting cells to adjust their secretion maintains the ionized calcium level of the ECF. The Mg^{2+} concentration is subject to close regulation, but the mechanisms controlling Mg^{2+} metabolism are incompletely understood.

The mechanisms controlling Na^+ and K^+ content are part of those determining the volume and tonicity of ECF and are discussed above. The levels of these ions are also dependent upon the H^+concentration, and pH is one of the major factors affecting the anion composition of ECF.

(Ref. Ganong 22th Edition; Page-730)

Defense of H^+ concentation : The mystique that envelopes the subject of acid-base balance makes it necessary to point out that the core of the problem is not 'buffer base' or 'fixed cation' or the like but simply the maintenance of the H^+ concentration of the ECF. The mechanisms regulating the composition of the ECF are particularly important as far as this specific ion is concerned, because the machinery of the cells is very sensitive to changes in H^+ concentration. Intracellular H^+ concentration, which can be measured by using microelectrodes, pH-sensitive fluorescent dyes, and phosphorus magnetic resonance, is different from extracellular pH and appears to regulate a variety of intracellular processes. However, it is sensitive to changes in ECF H^+ concentration.

The pH notation is a useful means of expressing H^+

concentrations in the body, because the H^+ concentrations happen to be low relative to those of other cations. Thus, the normal Na^+ concentration of arterial plasma that has been equilibrated with red blood cells is about 140 meq!L, whereas the H^+ concentration is 0.00004 meq/L. The pH, the negative logarithm of 0.00004 is therefore 7.4. Of course, a decrease in pH of 1 unit, eg. from 7.0 to 6.0, represents a ten-fold increase in H^+ concentration. It is important to remember that the pH of blood is the pH of ***true plasma***- plasma that has been in equilibrium with red cells- because the red cells contain hemoglobin, which is quantitatively one of the most important blood buffers.

(Ref. Ganong 22th Edition; Page-730)

H^+ Balance : The pH of the arterial plasma is normally 7.40 and that of venous plasma slightly lower. Technically, acidosis is present whenever the arterial pH is below 7.40, and alkalosis is present whenever it is above 7.40, although variations of up to 0.05 pH unit occur without untoward effects. The H^+ concentrations in the ECF that are compatible with life cover an approximately 5-fold range, from 0.00002 meq/L (pH 7.70) to 0.0001 meq/L (pH 7.00).

H^+ concentration and pH of body fluid :

	H^+ concentration		*pH*
	meq/L	*mol/L*	
Gastric Hcl	150	0.15	0.8
Maximal urine acidity	0.03	3x10-5	4.5
Extreme acidosis	0.0001	1x10-7	7.0
Plasma Normal	0.00004	4x10-8	7.0
Extreme alkalosis	0.00002	2x10-8	7.0
Pancreatic juice	0.00001	1x10-8	8.0

(Ref. Ganong 22th Edition; Page-731)

Amino acids are utilized in the liver for gluconeogenesis, leaving as products NH_4^+ and HCO_3^- from their amino and carhoxyl groups. The NH_4^+ is incorporated into urea and the protons that are formed are buffered intracellularly by HCO_3^-, so little NH_4^+ and HCO_3^- escape into the circulation. However, metabolism of sulfur-containing amino acids produces H_2S0_4, and metabolism of phosphorylated amino acids such as phosphoserine produces H_3PO_4. These strong acids enter the circulation and present a major H^+ load to the buftérs in the ECF.

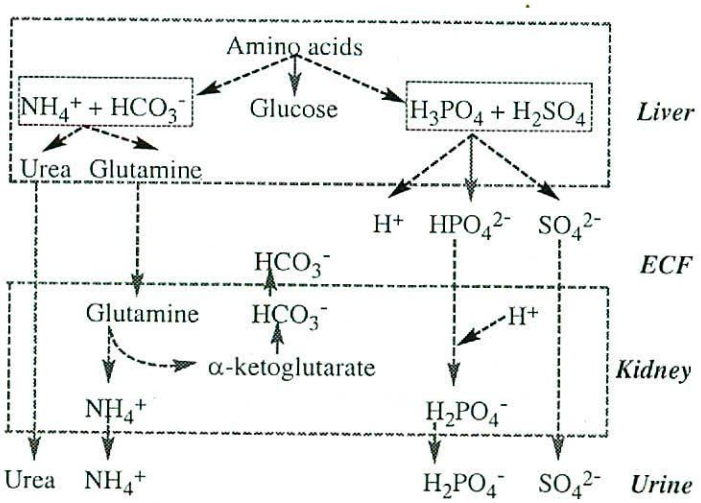
The H^+ load (causes of acdosis) from :

i. Amino acid metabolism is normally about 50 meq/day.
ii. The CO_2 formed by metabolism in the tissues is in large part hydrated to H_2CO_3 and the total H^+ load from this source is over 12,500 meq/day. However, most of the CO_2 is excreted in the lungs, and only small quantities of the H^+ remain to be excreted by the kidneys.
iii. Common sources of extra acid loads are-
   a. Strenuous exercise (lactic acid)
   b. Diabetic ketosis (acetoaeetic acid and beta-hydroxy butyric acid)
   c. Ingestion of acidifying salts such as NH_4CI and $CaCl_2$, which in effect add HC1 to the body.
   iv. Failure of diseased kidneys to excrete normal amounts of acid is also a cause of acidosis.

Causes of alkalosis : Fruits are the main dietary source of alkali. They contain Na^+ and K^+ salts of weak organic acids, and the anions of these salts are metabolized to CO_2, leaving $NaHCO_3$ and $KHCO_3$ in the body. $NaHCO_3$ and other alkalinizing salts are sometimes ingested in large amounts, but a *more common cause of alkalosis is loss of acid from the body as a result of vomiting of gastric juice rich in HCI.* This is of course equivalent to adding alkali to the body.

(Ref. Ganong 22th Edition; Page-731)

Role of the liver and kidneys in the handling of metabolically produced acids loads :



(Ref. Ganong 22th Edition; Page-731)

Directions : Write 'T' for true & 'F' for false against each of the following statement.

Q. 01. **Following are the ECF compartment :**
- T a. Plasma
- T. b. Pleural fluid
- T c. CSF
- T d. Synovial fluid
- T e. Peritonial fluid.

Q. 02. **Plasma concentration of ECF are as follows :**
- T a. Na^+ : 142 mEq/L
- T b. K^+ : 4 mEq/L
- T c. Ca^{++} : 2.4 mEq/L
- T d. Mg^{++} : 1.2 mEq/L
- T e. PO_2 : 35 mm of Hg.

Q. 03. **Plasma concentration of ICF are as follows**
- T a. Na^+ : 10 mEq/L
- T b. K^+ : 140 mEq/L
- T c. Ca^{++} : 0.0001 mEq/L
- T d. Mg^{++} : 58 mEq/L
- T e. PO_2 : 20 ?mm of Hg.

Q. 04. **Plasma concentration of the ECF are as follows :**
- T a. Cl^- : 103 mEq/L
- T b. HCO_3^- : 28 mEq/L
- T c. Phosphate : 4 mEq/L
- T d. PCO_2 : 45 mEq/L
- T e. SO_2^{--} : 1 mEq/L.

Q. 05. **Plasma concentration of ICF are as follows**
- T a. Cl^- : 4 mEq/L
- T b. HCO_3^- : 10 mEq/L
- T c. Phosphate : 75 mEq/L
- T d. PCO_2 : 46 mEq/L
- T e. SO_2^{--} : 2 mEq/L.

Q. 06. **Chemical composition of extracellar fluid are**
- T a. Cl^- : 108 mmol/Liter
- T b. protein : 2 mg/dL
- F c. Na^+ : 10 mmol/Liter
- F d. K^+ : 4 mmol/Liter
- F e. HCO_3^- : 10 mmol/Liter.

Q. 07. **Sodium ion concentration fall in plasma**
- T a. Reduces plasma osmolality
- T b. May result from xecessive production of ADH
- F c. Decreases intrcellular volume
- F d. Increases thirst
- F e. Increases the severity of oedema.

Q. 08. **Excessive sodium retension causes**
- T. a. Decrease renin production
- T b. Increase central venous presssure
- T c. Increase ADH secretion
- T d. Decrease aldosterone secretion
- F e. Loss of total body mass.

Q. 09. **Potasssium ion concentration in ECF**
- T a. Hyperkalaemia may cause cardiac arrest
- T b. Prolonged of Q-T interval occurs in hypokalaemia
- T c. It's uptake is increased by insulin
- F d. Aldosterone increase potassium reabsorption from the renal tubules
- F e. Potassium level in the ECF is decreased in acidosis.

Q. 10. **Chemical composition of intracellular fluid are**
- T a. Ca^{++} : 2.4 mmol/Liter
- T b. K^+ : 140 mmol/Liter
- T c. HCO_3^- : 24 mmol/Liter
- F d. Na^+ : 142 mmol/Liter
- F e. glucose : 0-20 mmol/Liter.

Q. 11. **Extra cellular fluid contains**
- T a. PO_2 : 35 mm of Hg
- T b. PCO_2 : 46 mm of Hg
- T c. Proteins : 2 gm%.
- F d. Na^+ : 145 mEq/dL
- F e. K^+ : 5 mEq/dL

Q. 12. **Intracellular fluid contains**
- T a. PO_2 : 20 mm of Hg
- T b. Na^+ : 10 mEq/L
- F c. K^+ : 125 mEq /L
- F d. PO_2 : 25 mm of Hg.
- F e. proteins : 10 gm%.

Q. 13. **Anion gap**
- T a. It is the difference between unmeasured anions and unmeasured cations

T b. Anion gap is increased in metabolic acidosis
T c. It is normally 10-18 mEq/L
T d. Anion gap detects the presence of acid-base disorder even in normal pH
F e. It is decreased in metabolic acidosis.

Q. 14. **Extracellular fluid**
T a. contains large amount of bicarbonate
T b. contains large amount of amino acid
T c. moves throughout the body
F d. contains large amount of potassium
F e. contains large amount of phosphate.

Q. 15. **Regarding osmotic presssure**
T a. It is the amount of pressure reqiured to prevent osmosis
T b. It is exerted by the nondiffusible solutes of the sodium
T c. Is decreased in hypoalbuminaemia
F d. Is directly proportionate to the mass of the solute
F e. Osmotic pressure of plasma is about 190 mosm/L.

Q. 16. **Regarding body fluid in a 70 kg adult male**
T a. Total body fluid is about 42 liters
T b. ICF is more than ECF
T c. Plasma volume is about 5% of the total body weight
T d. Total blood volume is about 8% of the total body weight
F e. Female has more body fluid than male due to excessive adipose tissue.

Q. 17. **Concerning body fluid**
T a. Interstitial fluid is an ultrafiltrate of plasma
T b. ECF has a greater osmotic strength than ICF.
T c. There is contineous loss of water via skin
F d. ECF has a higher H^+ concentration than ICF
F e. Plasma is an ICF.

Q. 18. **Features of alkalosis are**
T a. Tetany
T b. Overexcitation of nervous tissue
T c. Alkaline urine
F d. Hyperventilation
F e. Myocardial depression.

Q. 19. **Plasma**
T a. contain kallikrein.
T b. is the fluid portion of blood.
T c. is a remarkable solution containing ions.
F d. does not contain Hageman factor.
F e. is very much similar with serum.

Q. 20. **Plasma volume**
T a. helps to measure interstitial fluid volume.
T b. can be measured by ^{125}I-albumin
T c. can be measured by T-1824
F d. can be measured by ^{125}I-iothalamate
F e. can be measured by ^2H_2O

Q. 21. **Plasma volume can be measured by**
T a. direct method
T b. radioactive sodium
T c. radioactive iothalamate
F d. heavy water
F e. antipyrine.

Q. 22. **ECF volume is measured by**
T a. Renin-angiotensin-aldosterone system
T b. Vasopressin mechanism
T c. Thirst mechanism
T d. Epinephrine nor epinephrine mechanism
T e. Osmosodium receptor mechanism.

Q. 23. **D_2O is used to determine**
T a. Total body water
F b. ICF
F c. ECF
F d. Plasma volume
F e. All.

Q. 24. **Raised ECF K^+ levels seen in**
T a. Endolymph
F b. Ectolyrnph
F c. Aquous humour
F d. Vitreous humour
F e. All.

Q. 25. **In a man weighing 70kg, water content of body is :**
T a. 40-45 L
F b. 20-30 L
F c. 30-40 L
F d. 50-60 L
F e. 25-30 L.

Q. 26. **D_2O (Deuterium oxide) is used to measure volume of**
T a. Total body water
F b. Blood
F c. Extracellular fluid
F d. Intracellular fluid
F e. All.

Q. 27. **Regarding oedema**
T a. May be caused by malnutrition
T b. May be caused by increased vascular permeability
T c. Can be seen in liver disease
T d. Is caused by decreased plasma albumin concentration
T b. Means excess ECF volume.

Q. 28. **Body buffer**

T a. Acts by conversion of strong acid into weak acid
T b. They provide quick defense against acid-base disorder
F c. They can correct the acid-base disorder all the way back to normal
F d. Bicarbonate buffer is more powerfull than protein buffer
F e. They are mixture of weak acid and weak base.

Q. 29. **Regarding pH**

T a. pH is the negative logarithm of hydrgeon ion concentration to the base 10.
T b. pH of blood is directly proportionate to the PCO_2
T c. pH of urine is normally less than 7
F d. pH of arterial blood range from 7.2 to 7.6
F e. pH of blood is directly proportionate to the HCO_3^-

Q. 30. **The quantity of water lost as sweat per day is**

T a. 600 to 800 cc
F b. 100 to 200cc
F c. 1000 to 1200cc
F d. 300 to 400cc
F e. Above 1200 cc.

Q. 31. **A substance on I/V injection was found to be distributed through thirty percent of body water. It probably-**

T a. Did not enter cells of body
F b. Did not pass freely through blood capillaries
F c. Was distributed evently throughout body water
F d. Was excluded from CSF
F e. All.