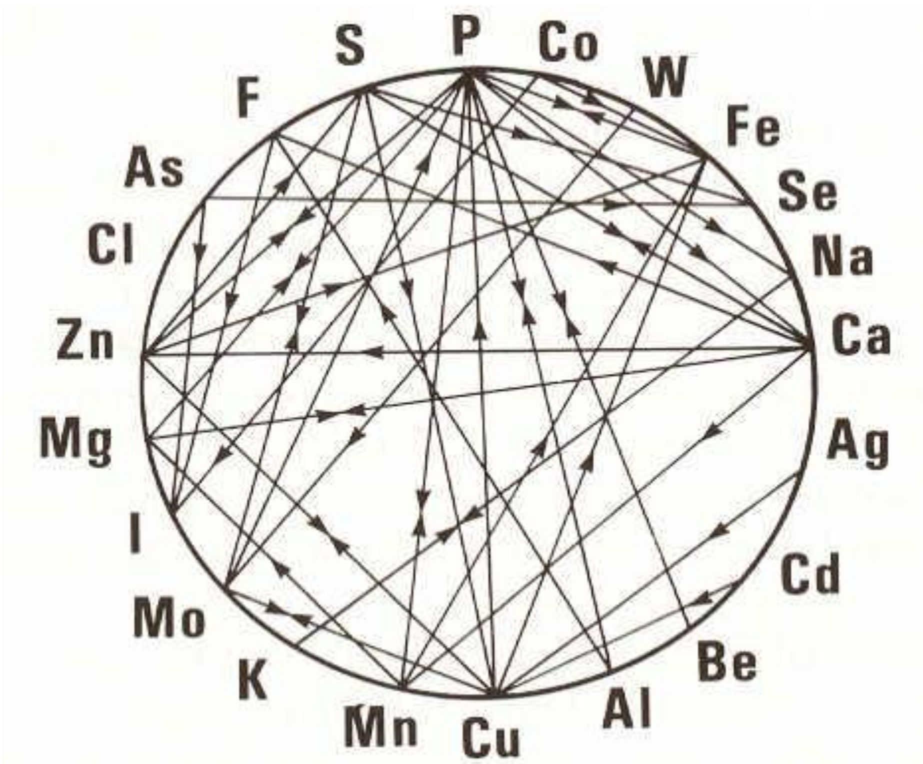


Mineral Metabolism

Introduction

What are Minerals?

Minerals

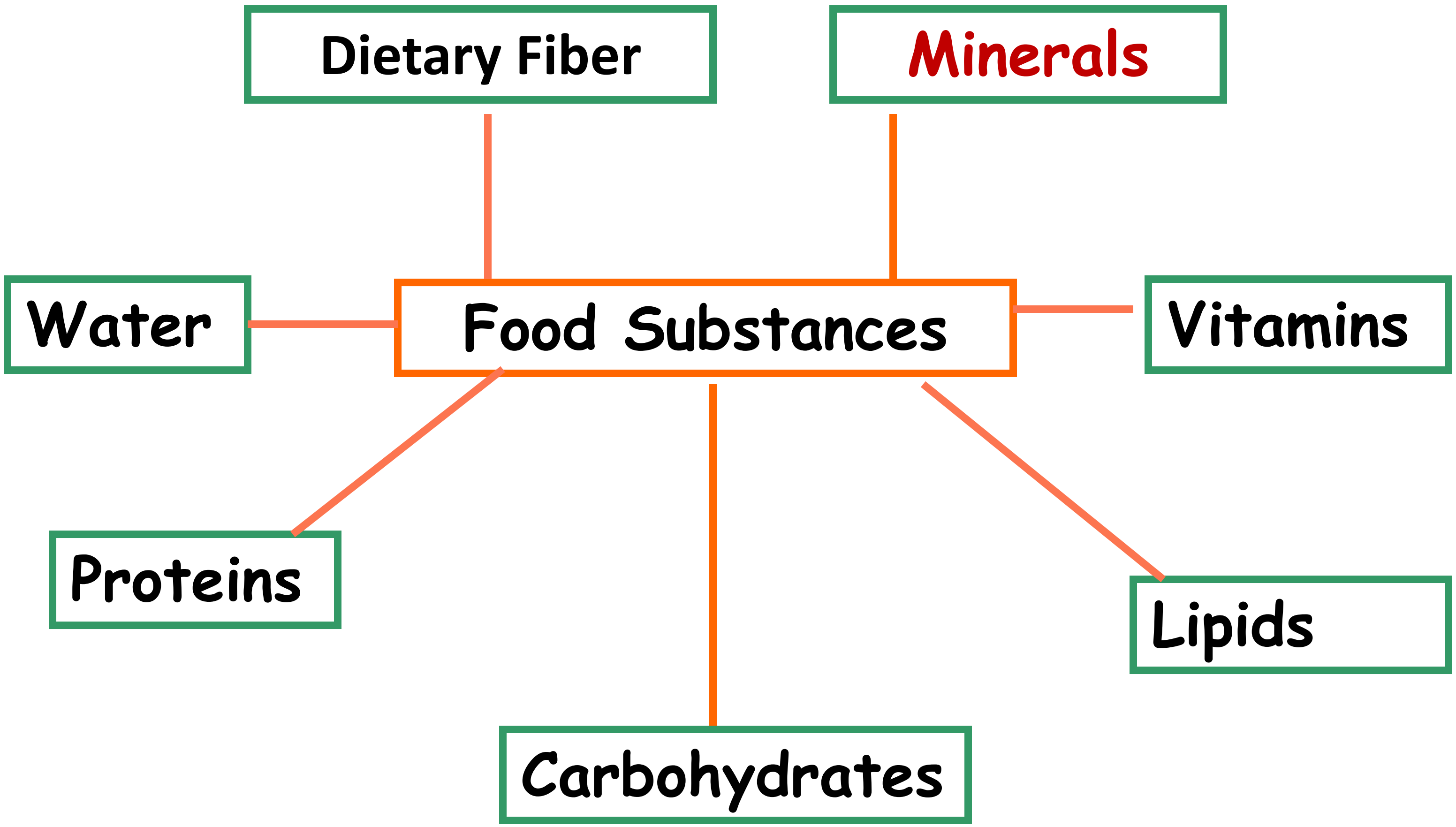
- **Minerals are Inorganic elements**
- **Not biosynthesized** in human body
- Widely distributed in nature
- **Present in foods** of **Plant and Animal** origin

Minerals In Human body

- Minerals in human body **serve for various structural and functional roles**

- Hence it **is essential to ingest** Minerals **through diet.**

Human Body Ingests Seven Food Nutrients



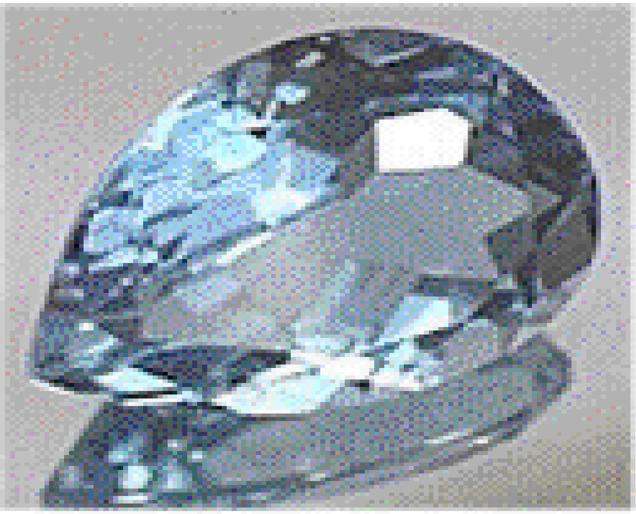
Minerals In Human body

- Minerals are Nutrient Of Human Food
  - Essential Nutrient
  - Micro Nutrient
  - Non Calorific Nutrient

Characteristics Of Minerals

Minerals

- **Natural** in Occurrence
- **Solid** in nature
- **Inorganic**
- **Definite chemical composition**
- **Crystal structure due to internal arrangement of atoms**



- Minerals ingested are **not changed in the body.**

- Minerals are **not destroyed by heat, light, acid or mixing**

Classification Of Minerals

Body Minerals

- 30 Chemical elements are identified as Minerals.
- Important for human growth, development and regulation of vital functions

- **Minerals are classified based on:**
  - ❖ **Functional need to body**
  - ❖ **Its daily requirement**

Two Broad Classes Of Minerals

- **Macro Minerals** – 60-80 %
- **Micro Minerals-** 20%

Macro/Principle/Chief Minerals

- **Body needs Macro Minerals relatively in large quantities**
- Minerals present in body tissues at concentrations **>50 mg/kg**
- Requirement of these Minerals is **>100 mg/day**

7 Names Of Macro/Chief Minerals

1. Calcium (Ca)
2. Phosphorus (P)
3. Sulfur (S)
4. Magnesium (Mg)
5. Sodium (Na)
6. Potassium (K)
7. Chloride (Cl)

- **Micro Minerals /Trace Elements**

- Body needs Micro Minerals **relatively in less amount**
- Present in **body tissues at concentrations <50 mg/kg**
- **Requirement** of these Minerals is < **100 mg/day**

Subclasses Of Micro/Trace Minerals

- Essential Trace Elements
- Possibly Essential Trace Elements
- Non Essential Trace Elements

Name Of 10 Essential Micro/Trace Elements

1. Iron (Fe)
2. Copper (Cu)
3. Cobalt (Co)
4. Chromium (Cr)
5. Fluoride (F)
6. Iodine (I)
7. Manganese (Mn)
8. Molybdenum (Mo)
9. Selenium (Se)
10. Zinc (Zn)

Possibly Essential Elements for Humans

Ni, Si, Sn, V, Ba, Li

Non Essential Trace Elements Of Humans

Pb, Hg, Al, Ag, Bo

Body Minerals

C H N O S P

Na K Ca Mg Cl

Biological forms of minerals in living systems

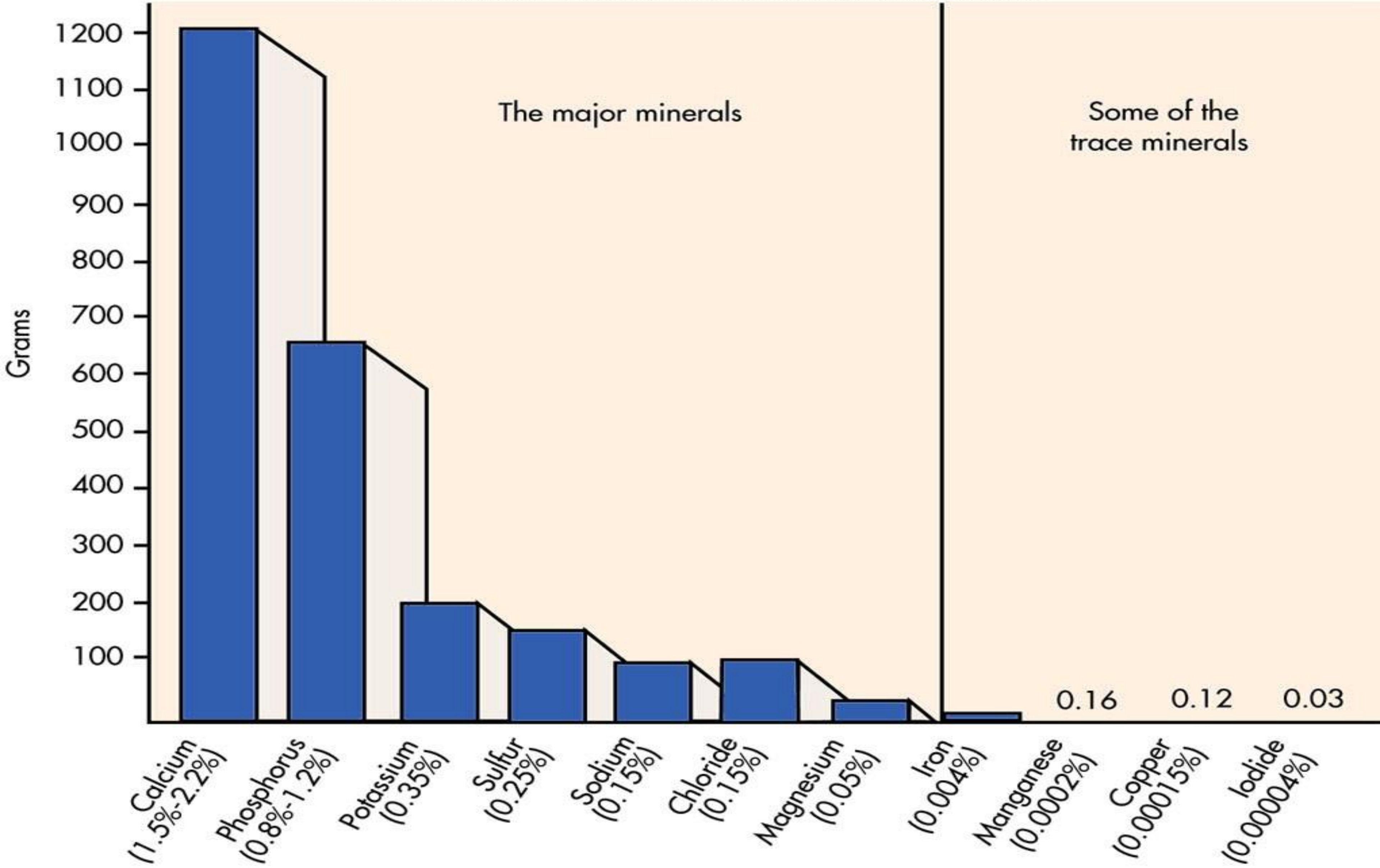
Fe Zn Cu Mn Se Co

V Si As Mo I Br F

Nutritionally Important Minerals

Macro Minerals		Trace Elements	
Element	g/kg	Element	mg/kg
Ca	15	Fe	20-50
P	10	Zn	10-50
K	2	Cu	1-5
Na	1.6	Mo	1-4
Cl	1.1	Se	1-2
S	1.5	I	0.3-0.6
Mg	0.4	Mn	0.2-0.5
		Co	0.02-0.1

Minerals in the Body



General Characteristic Features
Of
Human Body Minerals

Sources Of Minerals To Human Body

- **A mixed diet** of varied foods
- **Is the best source of Minerals**

Minerals in Foods

- Minerals are found in all food groups.

- More reliably found in
  - Fresh Fruits
  - Vegetables
  - Animal products

Factors Affecting Mineral Requirements

- **Form of Mineral fed -** Inorganic vs Organic forms
- **Interactions with other minerals**
- **Tissue storage**
- **Physiological State**

Site for Mineral Absorption

- Small intestine
- Large intestine

Variable Bioavailability of Minerals

Bioavailability Of Minerals

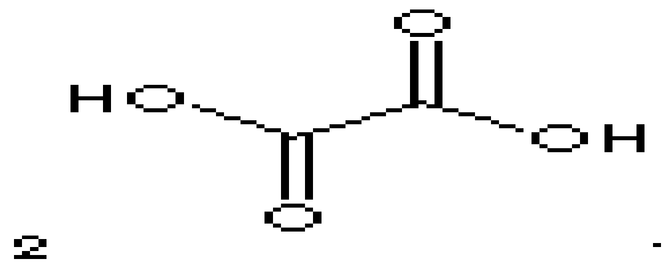
- **Bioavailability (absorption capacity)** of Minerals is influenced by :
  - **Genetics**
  - **Aging**
  - **Nutritional Status**
  - **Other food compounds**

Nutrient Interactions

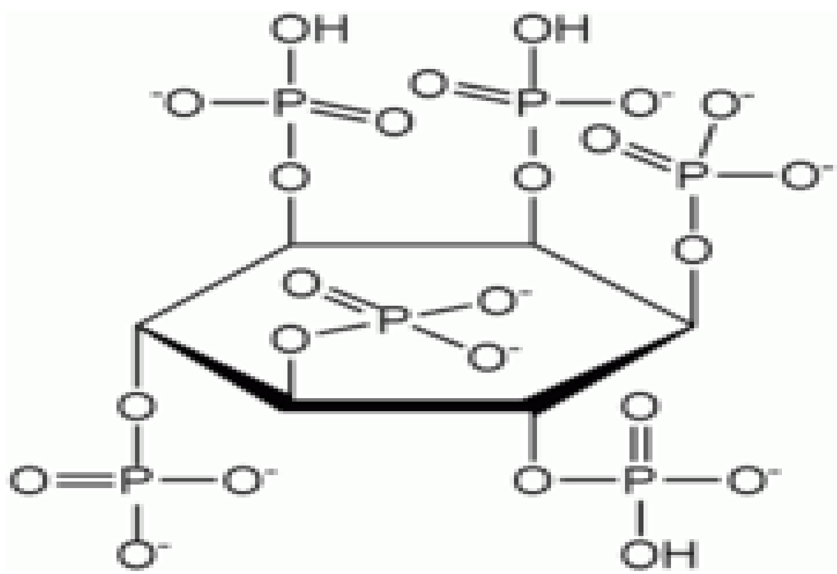
- Some **food components** bind with Minerals reducing their bioavailability

- **Mineral interactions** can affect another minerals absorption, and excretion

- Often other substances in foods decrease absorption (bioavailability) of Minerals:
  - **Oxalate,** found in spinach, **prevents absorption** of most **Calcium** in spinach.
  - **Phytate,** in most plants makes minerals poorly available



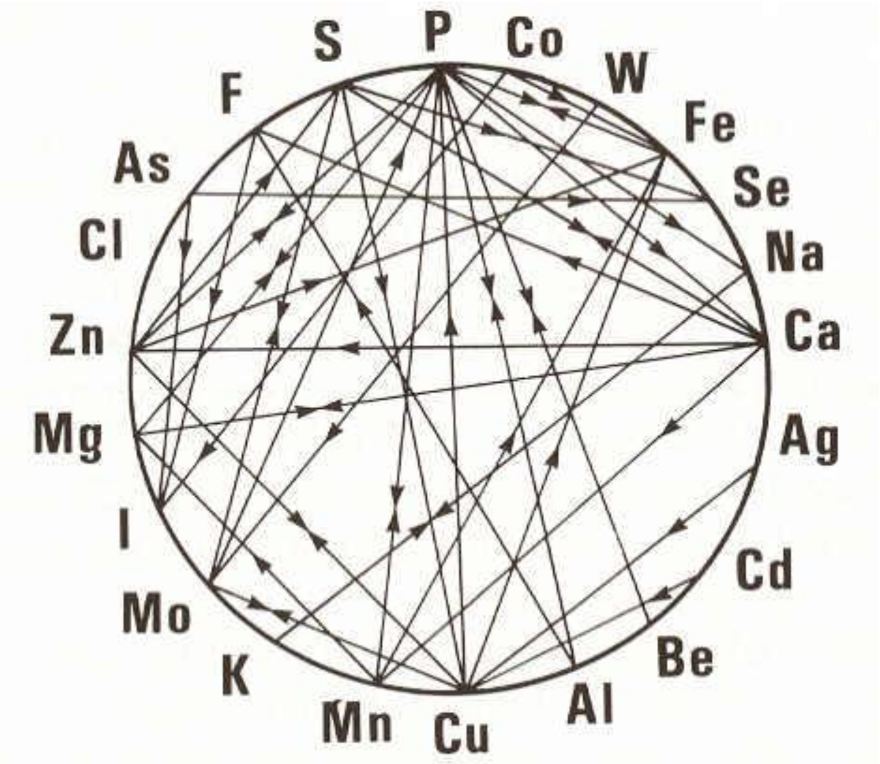
Oxalate



Phytate

Factors Affecting Requirements

- **Interactions with other Minerals**



- **Phosphorous binds with Magnesium** in the small intestine.

- So **Magnesium absorption is limited when Phosphorous intakes are high**

Uptake And Transportation Of Minerals

❖ Some **Minerals require no carriers to transport into intestinal wall.**

❖ **Some Minerals require carriers to enter** into intestinal wall.

- **Excretion and Regulation Site Of Minerals.**
  - Small intestine
  - Kidneys

General Functions of Minerals

- **Minerals with structural functions:**

  Ca, P ,Mg in bones; S in Keratin.

- **Minerals serve as Inorganic Cofactors:** participate with **Enzymes in metabolic processes .**

- **Role of Minerals in Acid-Base and Water balance: Na^+, K^+ and Cl^-**

- Minerals have role in Nerve & Muscle Function : Ca, Na, K, Mg

- Minerals are components of certain biomolecules:
  - Fe- Heme,
  - Co- Vitamin B_{12}
  - I_{2}- Thyroid hormones.

Mineral Deficiencies and Excesses

Mineral Balance

Minerals Inn=Minerals Out

- Most Minerals have an optimal range in blood/body.
  - Minerals below range leads to **deficiency symptoms**
  - Minerals above range leads to **toxicity symptoms**

- **Deficiency and excess of Minerals** in human body
- **Affect the normal health** and **vitality of human** body
- Which may lead to suffer from various manifestations.

Note

- Mineral content of soils
- Dictates Mineral status of plants.

- Mineral **deficiencies usually are rare**
- As they are widely distributed and essentially taken through food.

- However there are **many deficiency cases** noted of
- **Iron , Iodine and Calcium deficiencies**.

- It may take many **months to develop Mineral toxicity**.
  - The time taken to develop is **impacted by body stores.**

Study Of Specific Minerals

Study Of Macrominerals

Calcium Metabolism

- **Symbol** : **Ca^{+2}**
- **Divalent Cation**
- **Atomic Weight :** 40 g/mol
- **Atomic Number:** 20
- **Nature :**Soft Grey Alkaline Earth Metal

- Calcium is the **most essential abundant Macromineral** of human body.
- **Fifth most abundant element in Earth´s crust**

Calcium Occurrence In Nature

- **Naturally Calcium does not exist freely**

- Calcium occurs in form of Salts
  - **Limestone ($CaCO_3$)**
  - **Gypsum ($CaSO_4$*$2H_2O$)**
  - **Fluorite (CaF_2)**

Calcium In the Human Body

- Calcium is the **most abundant Macro Mineral**
- Average adult **body contains approx. 1.5 kg of Calcium.**

- **99%** of the body Calcium is **associated to skeleton** (Bones and Teeth).

- **1%** Calcium is **present in other tissues and body fluids.**

- **Calcium in bones is in dynamic state**

- **Calcium of bones may serve as large reservoirs storing excess Calcium**

- Bones **releases Calcium when extracellular fluid Calcium concentration decreases.**

RDA

Recommended Daily Amount Of Calcium

Calcium Dietary Requirements

– **Adult** : **800 mg/day**

– **Pregnancy, lactation and post-menopause:**
1500mg/day/1.5 g/day

– **Growing Children:** (1-18 yrs): **1200 mg/day**

– **Infants: (< 1 year): 300-500 mg /day**

Ca – Daily Requirements

Age/ sex	Ca (mg)
1-3	350
4-6	450
7-10	550
11-18 M	1000
11-18 F	800
19 +	700

Dietary Sources Of Calcium

Dietary Calcium sources

- **<u>Rich Calcium Sources</u>**

- **Milk and Milk Products**
- Millet (Ragi)
- Wheat-Soy flour
- Black strap molasses

Ragi/Red Millet/Finger Millet

- **Calcium Good sources**

- Yoghurt, sour cream, ice cream
- Tofu
- Gauva ,Figs
- Cereals
- Egg yolk
- Legumes

- Green leafy vegetables as collard, kale , Broccolli, Cabbage and raw turnip
- Small Fish as trout, salmon and sardines with bones
- Meat
- Almonds, brazil nuts, dried figs, hazel nuts
- Also soybean flour and cottonseed flour

Ca – Dietary Sources

- Milk – 100 ml =120mg
- Cheese – 15gm = 110mg
- **Yoghurt pot** – 80gm = **160mg**

Absorption Of Calcium

- Absorption of Calcium occurs in the **small intestine**
- In **Duodenum and first half Jejunum**

- Calcium must be in a **soluble and ionized form** for its **absorption**.

- **Calcium salts are unabsorbable forms.**

Calcium Absorption

- **Absorption depends on need of Calcium to body:**

- Particularly **high during growth, pregnancy and lactation**

Calcium Transport Mechanism Across Intestinal Mucosal Membrane

Ca Absorption Mechanism

- Simple diffusion/Passive
- An active transport involving Ca pump

Calcium Passive Transport

- Is a non saturable, paracellular
- It is less efficient process
- Is not affected by calcium status or parathyroid hormone

•Active Absorption of Calcium:

- Against electrical and concentration gradient, by an **energy dependent active process.**

Calcium Active Transportation

- Regulated by the active form of **Vitamin D/Calcitriol.**

- Which involves **Calbindin** (Calcium-Binding Protein) –

Factors Promoting Calcium Absorption

Parathyroid Hormone (PTH) indirectly enhances Ca absorption through the increased activation of Calcitriol.

Calcitriol

- **Calcitriol /activated Vitamin D , induces the synthesis of Ca binding protein Calbindin**

- **Calbindin in the intestinal epithelial cells then promotes Ca absorption.**

Acidity (low pH)

- **Acidity is more favorable for Ca absorption.**
  - **Calcium salts are soluble in acid solutions**
  - **So acidity increases the absorption of Calcium.**

- **Lactose** , **Citric acid promotes Calcium uptake by intestinal cell.**

- **Amount of Proteins in Diet:**
- **Amino acids Lysine and Arginine form soluble complexes with Calcium**
- **Hence high protein diet favors the absorption of Calcium.**

- **Concentration of Calcium in diet:**

- **Higher the concentration of Calcium**
- **More is the absorption of Calcium.**

Factors Inhibiting Calcium Absorption

- **Phytates and Oxalates present in plant origin diet form insoluble salts and interfere with Ca absorption.**

- **The high content of dietary Phosphates results in the formation of insoluble Ca phosphate and prevent Ca uptake.**
  - **Dietary ratio of Ca : P ---1:1 / 2:1**
  - **is ideal for Ca absorption.**

- The **Free Fatty acids** react with Ca to form insoluble Ca soaps.

- The Alkaline condition (high pH) is unfavorable for Ca absorption.

- **Low Estrogen levels in postmenopausal women lowers Calcium absorption.**
- **Since Estrogen increases Calcitriol levels**

- **High content of Dietary fiber,Caffeine,Sodium interferes with Ca absorption.**

- **Amount of Magnesium in diet:** **Excess Magnesium in diet inhibits Calcium absorption.**

- **As Magnesium competes with Calcium for absorption.**

Calcium
Absorption and Excretion at GIT

- Usual Ca intake is1000 mg/day.
- About 35 % is absorbed (350 mg/day) by the intestine.

- Remaining Calcium in the intestine is excreted in the feces
- 250 mg/day enters intestine via secreted gastrointestinal juices and sloughed mucosal cells

90 % (900 mg/day) of the daily intake is excreted in the feces

10 % (100 mg/day) of the ingested calcium is excreted in the urine.

Body Distribution Of Calcium

- **Total content of Calcium** in an **Adult body is 1-1.5 Kg.**

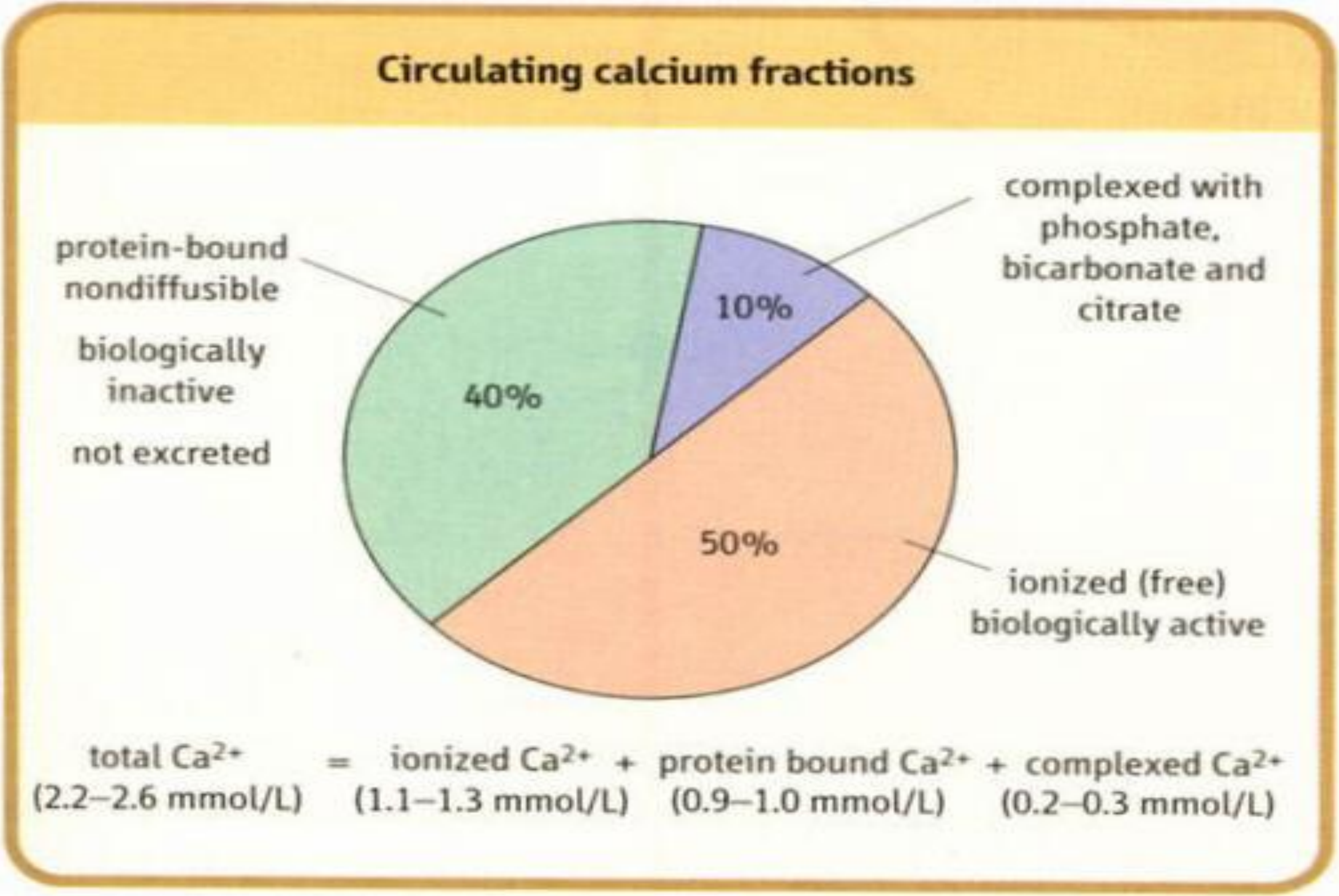
- Calcium constitutes **2% of total body weight.**

BODY CALCIUM

- **99%** of Calcium is in **Bones**
- **0.8%** of Calcium is in **soft tissues** (ICF)
- **0.1%** in **Blood** (ECF)

PLASMA CALCIUM

Three Forms of Circulating Ca^{2+}



Diffusible Calcium

- **50% Ca^{2+} Ionized/Physiologically active form.**

- **10% combined with anions** (Citrate, Phosphate) –Non-dissociated/Non ionizable form.

Non diffusible Calcium

- 40% **combined with plasma proteins**

- Combination with proteins depends on pH 0.2 mmol/l ,Ca^{2+} on each pH unit

Blood Calcium Levels

- The normal serum total calcium is:
  - **9-11 mg/dL**
  - **2 -3 mmol/L**

- **Normal levels** of the ionized/free/diffusible/**physiological form of Calcium is**
  - **4.5-5.6 mg/dL**
  - **1.1-1.4 mmol/L**

- **Protein bound Calcium** (Mostly bound to Albumin)/Non diffusible/Bound form of Calcium: **4 mg%.**

- **Calcium Salts** /Bound form/Inorganic Salts/Diffusible:
- Calcium Phosphate and Calcium Citrate=**1mg%**

Erythrocytes Almost Contain No Calcium

Calcium In Alkalosis

- **Alkalosis favors binding of more Calcium with Proteins.**
- **This consequently lowers ionized Calcium.**

Acidosis Favors Ionization of Calcium

Multiple Biological Functions of Calcium

- Calcium is **widely distributed in the body**
- Involved **with many functions** to keep the **body vital and active**.

1. Structural Role Of Calcium

- Calcium is a **major structural element** in the vertebrate skeleton forms **bones and teeth**.

- **Calcium along with Phosphorous, Magnesium** forms **the inorganic matrix of the bone** as **Hydroxyapatite crystals**
- Which gives the **tensile strength to the bones and teeth**.

- In the form of Calcium Phosphate($Ca_{10}(PO_4)_6(OH)_2$ known as **Hydroxyapatite**

- **Osteoblasts** are responsible for **bone formation**

- While **Osteoclasts** are for **bone resorption.**

- Bones undergo **mineralization** during **osteoblastic activity**

- **Demineralization** during **osteoclastic activity.**

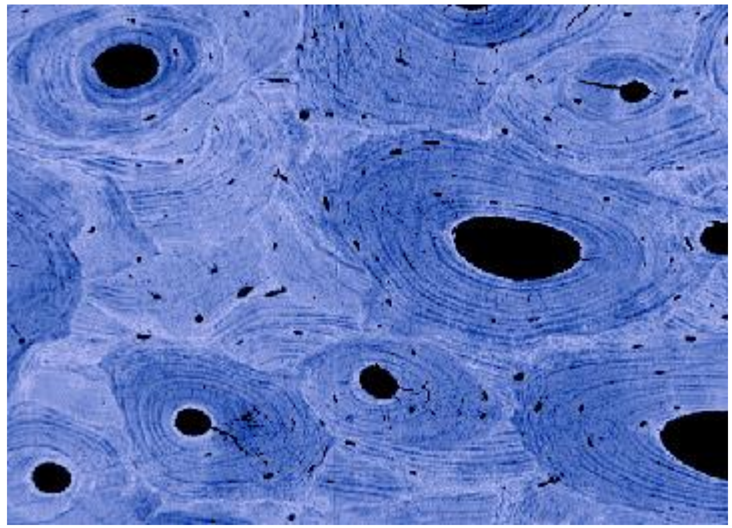
Bone Act As Major Reservoir Of Calcium

- **Osteoclasts secrete acid**, causing the **release of calcium and phosphate into the bloodstream**.

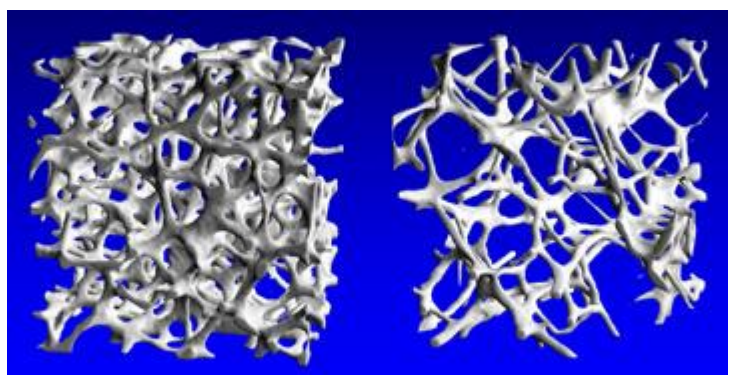
- There is **constant exchange of calcium between bone and blood.**

Leg bone of a horse showing the trebecular (spongy) bone and the cortical (solid) bone. This bone is able to withstand forces generated by this 1,500 lb animal

Cross section through trebecular and cortical bone revealing the internal architecture surrounded by marrow tissue.

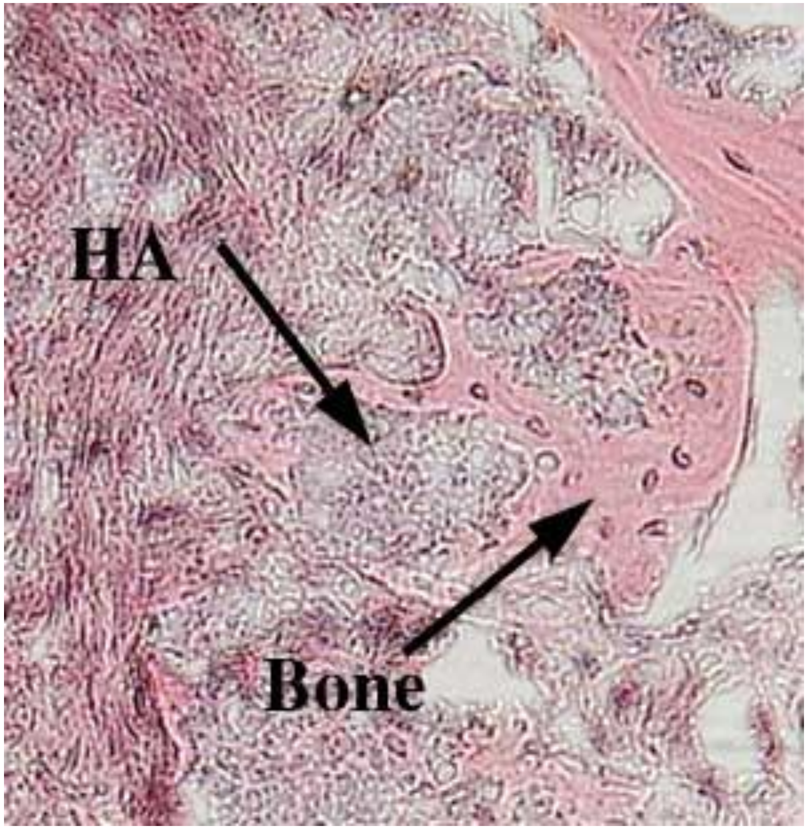


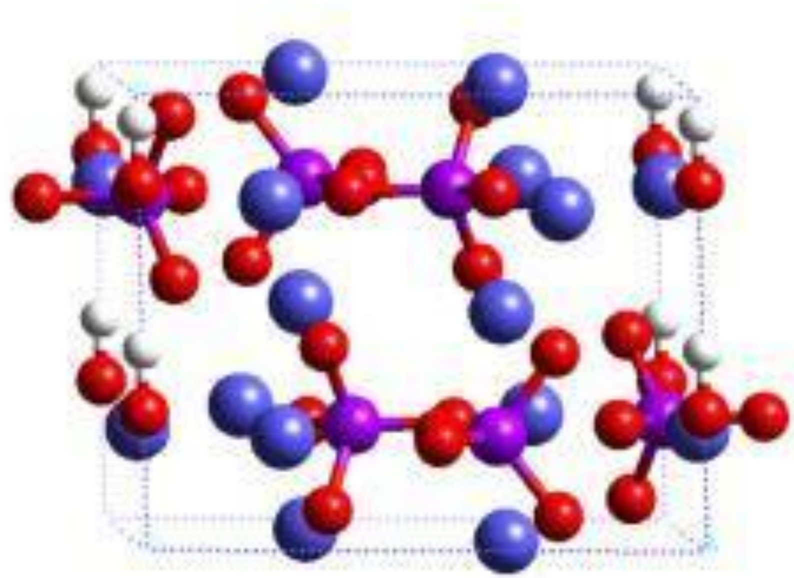
Cortical bone with Halversion system (a series of channels supplying nutrients). Black dots are osteocytes



Trebecular bone of the lower spine. Changes with aging.

Demineralized bone: Shown is the organic matrix consisting mostly of collagen upon which the bone crystals are laid.





Hydroxyapatite (crystal structure)

$Ca_{10}(PO_4)_6\ OH_2$

Ca P O H

Remember/Note

- During **growth , pregnancy and lactation phase**
- To give **strength for building bones and teeth.**
- One should take **adequate amounts of dietary Calcium and Phosphorous**

2. Calcium Role in Muscle Contraction

- The **ionized free form of Calcium** interacts with

- **Muscle Protein Troponin C** to **trigger muscle contraction.**

- Calcium also **activates Ca-ATP ase** and **increases the interaction between Actin and Myosin** during muscle contraction.

- Thus Calcium has **role in excitation and contraction of muscle fibers.**

3. Role Of Calcium In Nerve Impulse Conduction

- **Ionized Calcium transmits nerve impulses**

- **From pre-synaptic to post-synaptic region.**

4. Role of Calcium in Hormonal Actions

- Calcium **serves as second and third messenger** for certain hormonal activities.
- **Calcium –Calmodulin complex** mediates the hormonal action.

- **Calmodulin** is a Calcium binding regulatory Protein which binds with **4 Calcium ions.**

- **Calmodulin serve as messenger** during hormonal action by **stimulating Protein Kinases.**

- **Epinephrine** require Calcium as **second messenger** at the time of its action.
- **ADH** require Calcium as **third messenger** during its action.

5. List Of Enzymes Activated By Calcium and Mediated By Calmodulin

- Adenyl Cyclase
- Glycerol-3-PO4 Dehydrogenase
- Glycogen Synthase
- Pyruvate Carboxylase
- Pyruvate Dehydrogenase
- Pyruvate Kinase

6. Calcium as Chelating Agent In Blood Clotting Mechanism.

- Calcium as **Clotting factor IV** serves as a cofactor for several reactions in the **Cascade of blood clotting process.**
- Calcium serves as **chelating agent during Thrombin formation.**

7.Calcium act as a Cofactor of Enzymes

- Calcium serve as an inorganic cofactor of: **(Direct action)**
  - **Pancreatic Lipase**
  - **ATPase**
  - **Succinate Dehydrogenase**

8.Calcium Role in Secretion of Hormones

- Calcium stimulates to **release of following Hormones:**
  - **PTH**
  - **Insulin**
  - **Calcitonin**
  - **Vasopressin/ADH**

9.Calcium Transport Across The Biomembranes

- The **cell membrane is generally impermeable to Calcium ions**.

- **Calcium influx into cells** is **via Calcium channels by Na /Ca exchange mechanism.**

- There are different **Calcium Channels located** in the membranes of various cell organelles.

10. Calcium Prolongs Systole

- Calcium acts on Heart and **prolongs Systole**.
- **Hypercalcemia may lead to Cardiac arrest in Systole.**

Remember

- When Calcium is administered intra venously
- It should **be infused very slowly to avoid the cardiac arrest.**

11.Calpains – Calcium Dependent Cysteine Proteases

- **Calpains** are **involved in:**
  - **Cell mobility**
  - **Cell cycle progression**
  - **Cell membrane fusion events**

- Cell fusion in Myoblasts
- Neural vesicle Exocytosis
- Platelet aggregation

- **Increased concentration of Calcium** in cells.

- **Increases Calpain activation.**

- **Increased Calpains** causes **unregulated proteolysis .**

- **Hyperactivity of Calpains** consequent **leads to irreversible tissue damage.**

- Calcium is a key component in the **maintenance of the cell structure**
- **Membrane rigidity, permeability and viscosity** are partly dependent on local calcium concentrations

- 11. Calcium promotes

- Transportation of water and ions across the membranes.

- Excitability of cell membranes.

- Calcium regulates **cellular secretory process** such as :
  - **Endocytosis**
  - **Exocytosis**
  - **Cell motility**

- **Calcium has role in:**
  - **Cell to Cell contact**
  - **Cell to cell communication**
  - **Cell adhesion in tissues**

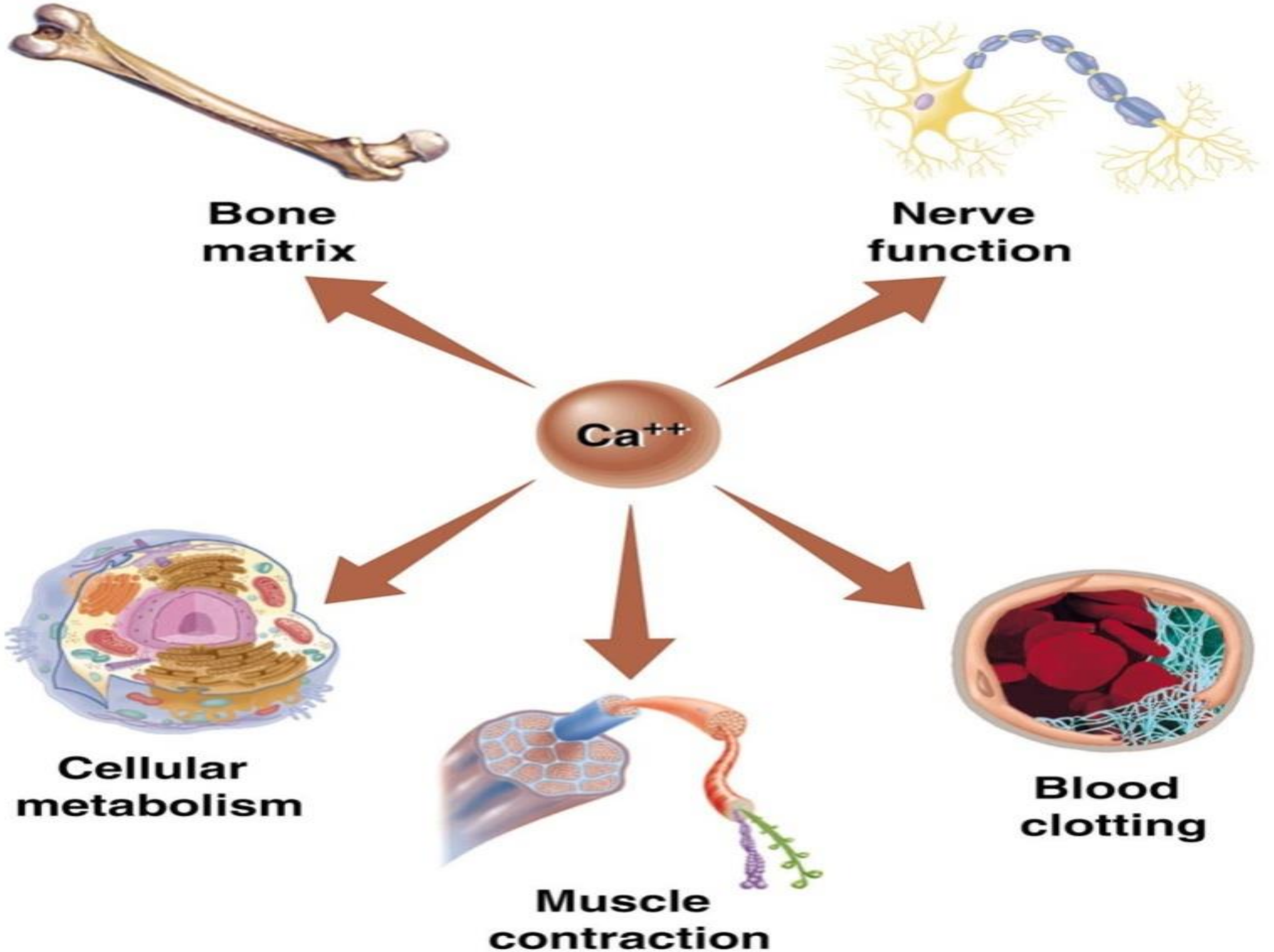
- Calcium is added to **mothers milk during lactation phase** of women.

Calcium Active Role:

- In the **relaxation and constriction of muscles**
- In **nerve impulse transmission**
- As an **intracellular signal**
- In **cell aggregation and movement**
- In **secretion of hormones**
- In **cell division**

Calcium Passive Role:

- As a **cofactor** for many enzymes (e.g. Lipase) and proteins
- As **component in the blood clotting cascade**



Bone matrix
Nerve function
Ca++
Cellular metabolism
Muscle contraction
Blood clotting

Homeostasis Of Blood Calcium

OR

Regulation of Blood Calcium

- The normal levels of **total serum Calcium is 9-11 mg%.**
- It is **very essential to maintain the constant range of Calcium.**
- For normal health and survivallence of human body.

- Most important is the **ionized or physiological form of Calcium present** in blood

- This **plays an important roles in various physiological and metabolic functions of human body.**

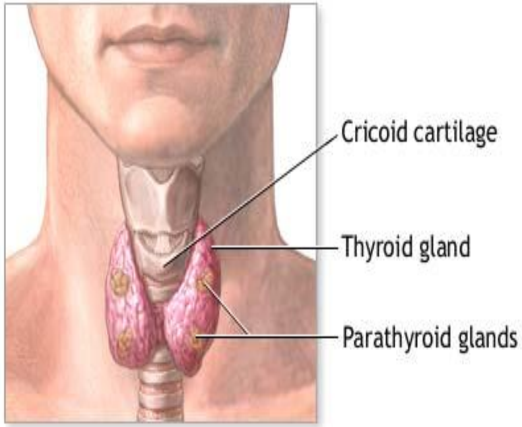
- **Maintenance of calcium homeostasis.**
  - **Regulation in dietary absorption**
  - **Storage**
  - **Excretion** of Ca

Factors Regulating Blood Calcium Levels

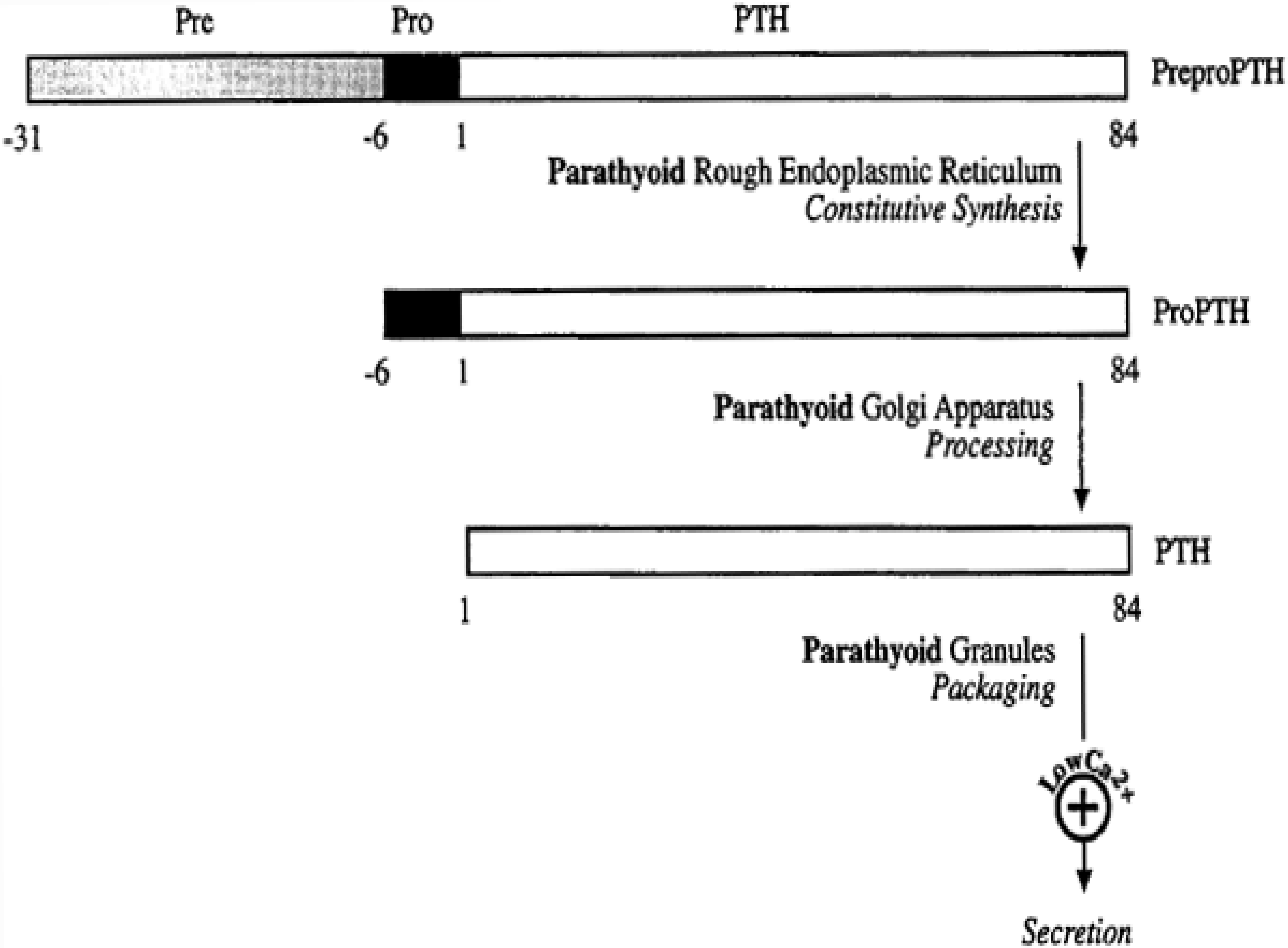
- Parathyroid Hormone (PTH)
- Vitamin D- Calcitriol
- Calcitonin

- The PTH , Calcitriol and Calcitonin **cooperatively works**
- To **regulate the transiently increased** and **decreased** levels of **serum Calcium** .

Parathyroid hormone (PTH)



- PTH is secreted by two pairs of **parathyroid glands.**
- PTH is initially synthesized as a precursor, **preProPTH.**
- Two proteolytic cleavages produce the **ProPTH** and the secreted form of **PTH (84 aa).**


Pre
Pro
PTH
PreproPTH
-31
-6
1
84
Parathyoid Rough Endoplasmic Reticulum
Constitutive Synthesis
ProPTH
-6
1
84
Parathyoid Golgi Apparatus
Processing
PTH
1
84
Parathyoid Granules
Packaging
LowCa2+
Secretion

- The **secretion of PTH are promoted**
- By low Ca^{2+} concentration in blood.

Regulation of PTH Secretion and Biosynthesis

- **Extracellular Ca^{2+} regulates secretion of PTH**
  - Low Ca^{2+} increases PTH levels
  - High Ca^{2+} decreases PTH levels

Mechanism of action of PTH

- PTH is **the most important endocrine regulator of Ca and Phosphorous** concentration.
- Function:
  - **Elevate serum Ca level**.

- **PTH** has **3 independent tissues to exert its action.**
  - **Intestine (Indirectly)**
  - **Bone (Directly)**
  - **Kidney (Directly)**

- **PTH Regulates through 3 Main Effects:**
  - Stimulating activation of vitamin D → ↑ **intestinal Ca absorption**
  - **Stimulating bone resorption**
  - **Increasing renal tubular calcium reabsorption**

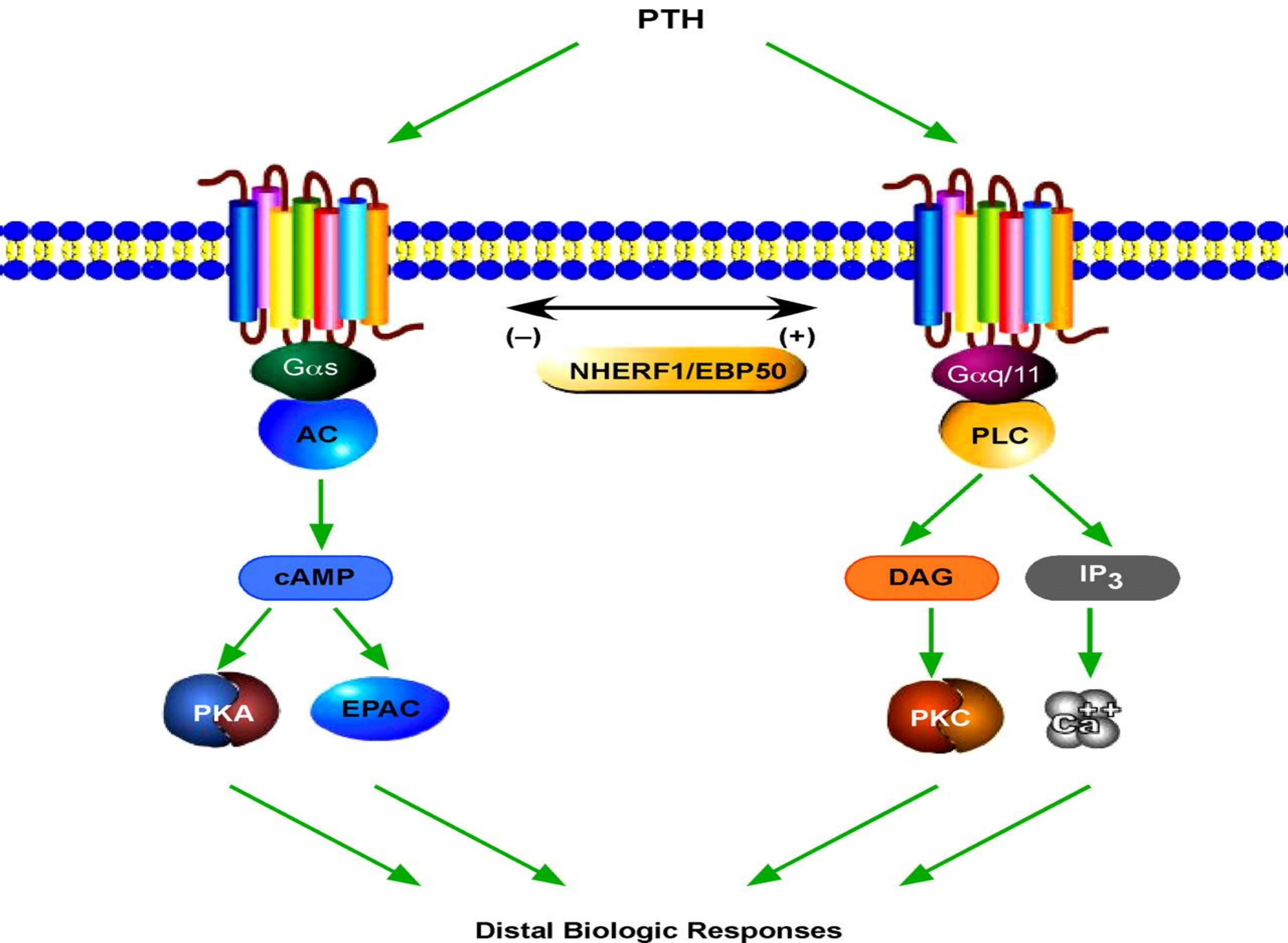
Actions of Parathyroid Hormone On Bone

- **Parathyroid hormone acts directly on bone** to **stimulate resorption**
- **This releases Ca^{2+} into the extracellular space and fluids** (slowly)

PTH Action on the Bone

- **Decalcification or Demineralization** of bone, **carried out by osteoclasts.**
- →blood Ca level ↑
- Note: this is being done at the expense of loss of Ca from bone, particularly in **dietary Ca deficiency**.

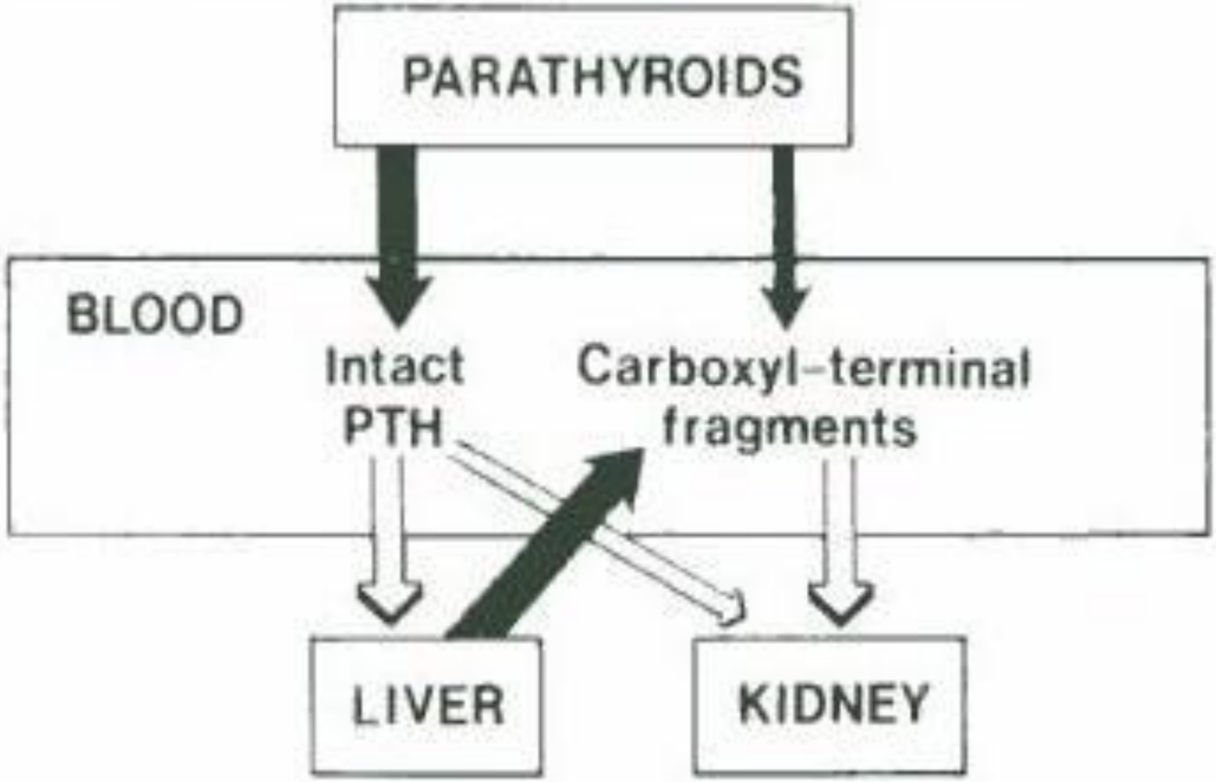
- **Gs protein-coupled receptors** in osteoblasts increase cAMP and activate **Protein Kinase Activity** (PKA)
- This **Inhibits osteoblast function**
- This occurs when PTH is secreted continuously.



PTH
(–)
(+)
NHERF1/EBP50
Gαs
AC
cAMP
PKA
EPAC
Gαq/11
PLC
DAG
IP3
PKC
Ca++
Distal Biologic Responses

Circulating Forms of PTH

Secretion and metabolism of intact PTH and carboxyl-terminal fragments. Secretion is indicated by solid arrows, and major directions of metabolism by open arrows.

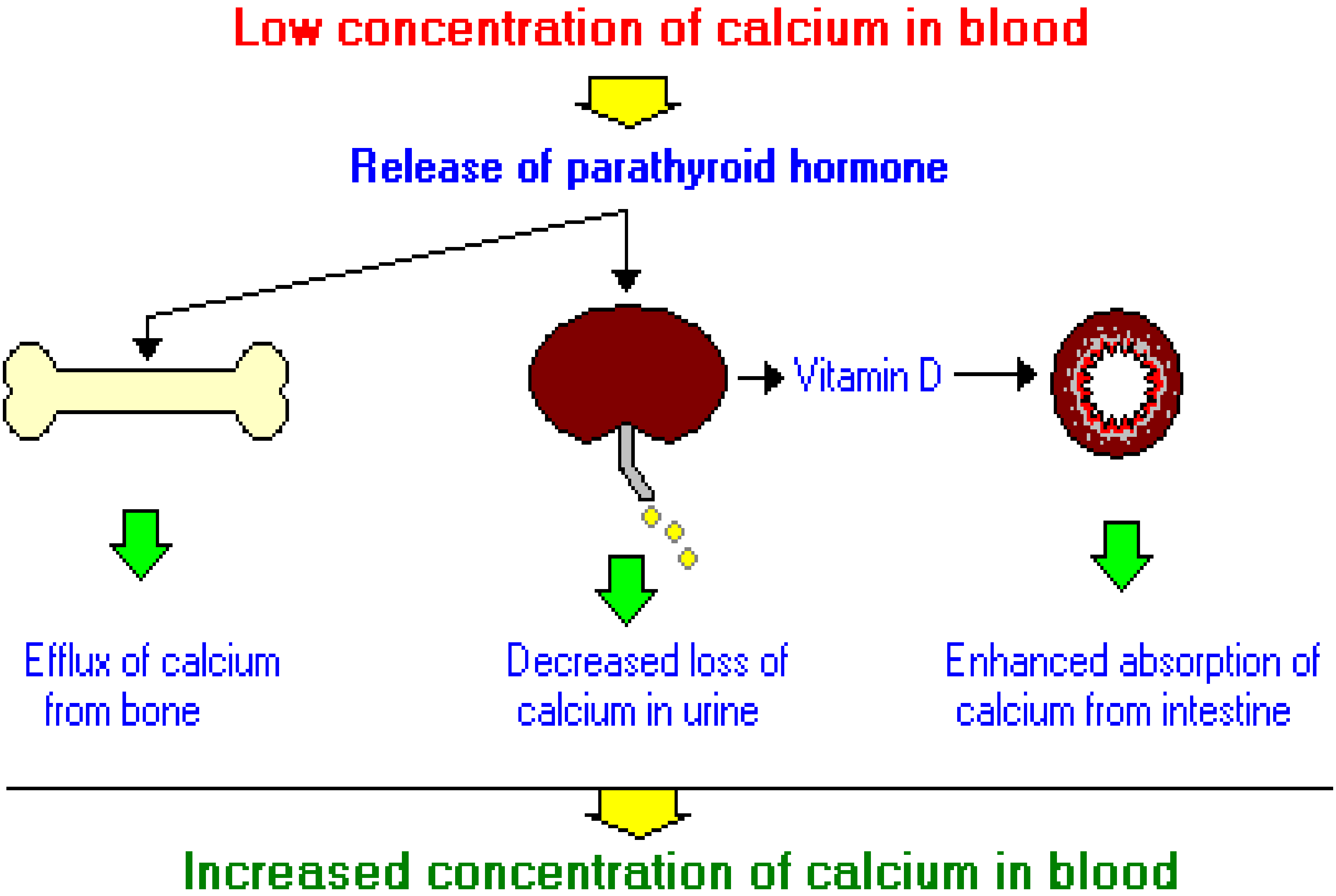


Action Of PTH
on the Kidney and Intestine

- Action on the **Kidney**: increase the Ca reabsorption.
- Action on the **Intestine**: **indirect,** increase the intestine absorption of Ca **by promoting the synthesis of Calcitriol**.

- **PTH Effects in Kidney**
  - Parathyroid hormone acts directly on kidney
  - To increase calcium reabsorption and phosphate excretion (rapid)

- Gs protein-coupled receptors
- Parathyroid hormone acts on **distal tubule**
- **Increases renal reabsorption of Calcium.**
- **Adds Calcium to blood regulating its levels.**

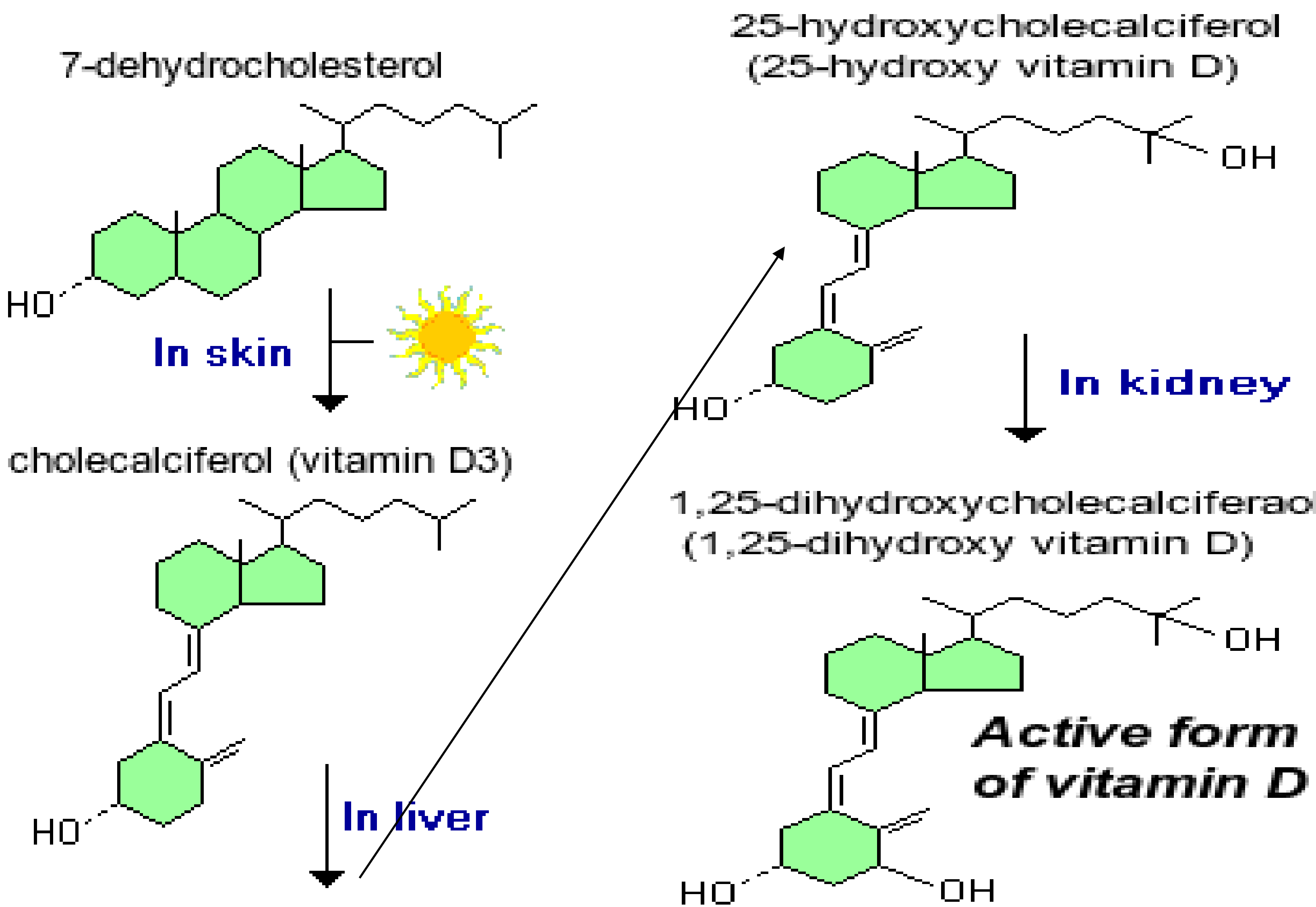

Low concentration of calcium in blood
Release of parathyroid hormone
Vitamin D
Efflux of calcium from bone
Decreased loss of calcium in urine
Enhanced absorption of calcium from intestine
Increased concentration of calcium in blood

Role Of Calcitriol/ Activated Vitamin D

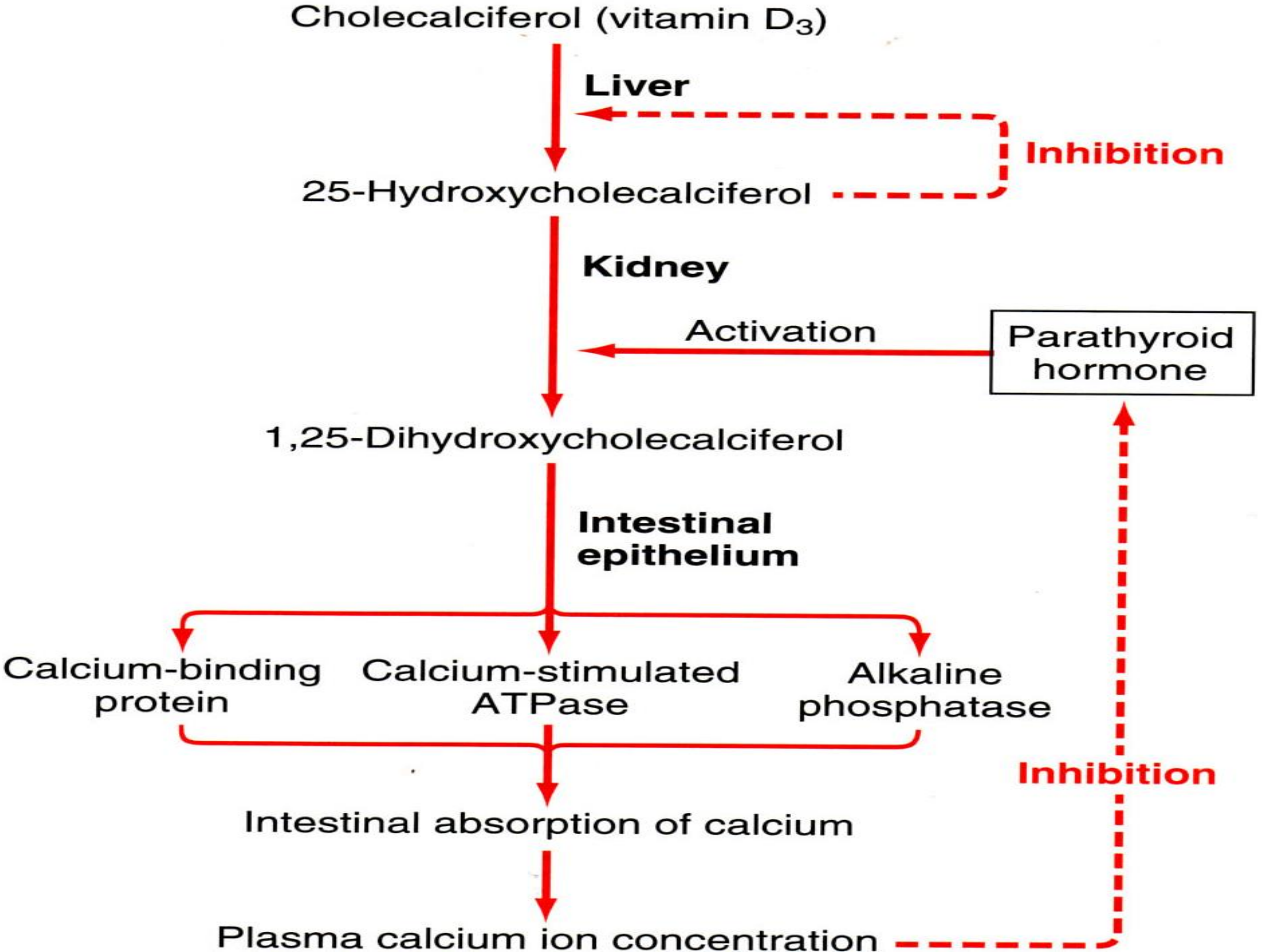
- Calcitriol several effects on the intestine and kidneys that increase absorption of calcium and phosphate into the extracellular fluid
- Important effects on bone deposition and bone absorption

PTH and Calcitriol By their Activity Increases Blood Calcium Levels

- Calcium levels below subnormal levels
- Stimulates the secretion of PTH
- PTH then stimulates the Vitamin D activation to Calcitriol.



Calcitriol (1,25-dihydroxy-cholecalciferol, 1,25 DHCC)



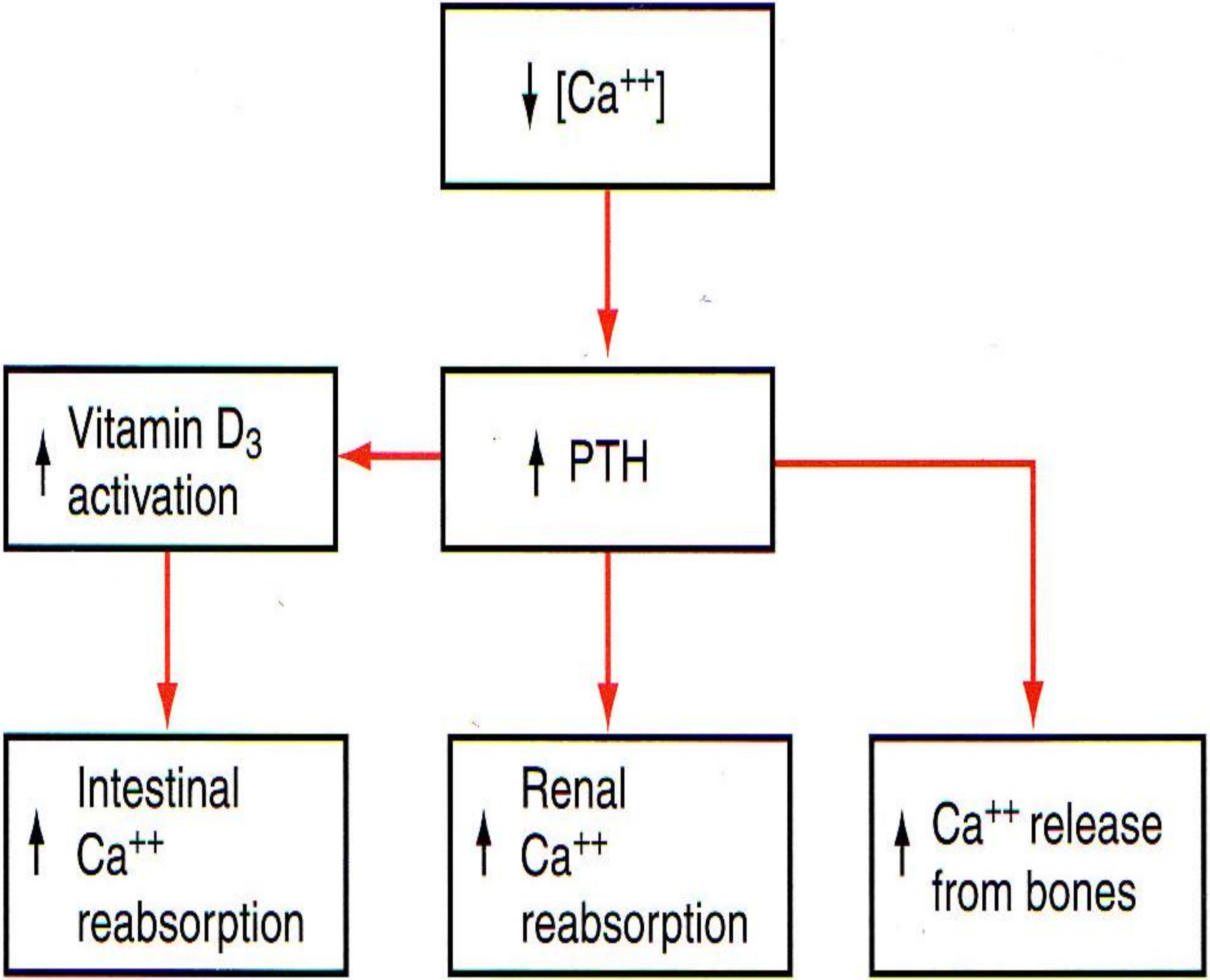
Cholecalciferol (vitamin D3)
Liver
Inhibition
25-Hydroxycholecalciferol
Kidney
Activation
Parathyroid hormone
1,25-Dihydroxycholecalciferol
Intestinal epithelium
Calcium-binding protein
Calcium-stimulated ATPase
Alkaline phosphatase
Inhibition
Intestinal absorption of calcium
Plasma calcium ion concentration

Activation of Vitamin D_3

- **Cholecalciferol** formed in the skin by sun
- Converted in liver and Kidney to

- **1,25 DHCC Controlled by PTH**
- Plasma calcium concentration inversely regulates 1,25 DHCC

- PTH and Calcitriol then acts on three target organs
- They try to increase the blood Calcium levels by their **Hypercalcemic action.**



↓ [Ca++]
↑ PTH
↑ Vitamin D3 activation
↑ Intestinal Ca++ reabsorption
↑ Renal Ca++ reabsorption
↑ Ca++ release from bones

Action On Intestinal Mucosal cells

- **Calcitriol** enters **intestinal mucosal** cells.
- **Acts like Steroidal hormone**
- Stimulate the **biosynthesis of Calbindin a Calcium binding Protein by gene expression.**
- Calbindin binds with dietary Calcium in GIT, **promotes it absorption and diffuse in blood.**

Calcitriol Action On Renal Tubules

- **Calcitriol** acts on **renal tubules** and increases tubular renal absorption of Calcium from plasma ultra filtrate there by **decreasing excretion of Calcium**.
- The **reabsorbed Calcium by renal tubules** add **Calcium to blood these by increasing blood Calcium levels.**

Action On Bones

- **PTH hormone directly acts on bones** causing decalcification of bones
- To release bound form of Calcium into free form**, catalyzed by increased activity of ALP**
- Which increases the levels blood Calcium to blood there by increasing blood Calcium levels to attain a normal level of 9-11 mg%

Remember

- The **low intake of dietary Calcium** may **increase the bone resorption** by **PTH to regulate blood Calcium levels.**

- This **may decrease the blood Calcium content of bones**
- **Leading to weakness in bones manifesting bone pain and recurrent bone fractures.**

Calcitonin

- **Calcitonin** a peptide hormone (32 aa) secreted by the **parafollicular cells of Thyroid gland**

- Calcitonin tends **to decrease plasma Calcium concentration**

Role Of Calcitonin In Decreasing The Blood Calcium Views

- When ever the blood Calcium goes **above 11 mg%**
- The **Calcitonin by its Hypocalcemic action**
- Tries to lower the increased the blood Calcium levels.

- **Calcitonin** promotes the **bone mineralization or Calcification of bones**.

- The **blood Calcium is taken up by bones and reserved.**

- Thus **Calcitonin increases Osteoblasts activity**
- **Enhances bone mineralization**.
- **Promotes bone growth**
- **Reduces increased blood Calcium levels to attain 9-11 mg%.**

- **Calcitonin adds Calcium to bones** and **increases bone mineralization**.

Role Of Calcitonin (CT)

- CT has the ability **to decrease blood Ca and P** levels and its major target cells also in bone, kidney and intestine.

1. **Bone:** Stimulate **Osteogenesis.**
2. **Intestine:** Inhibit absorption of Ca.
3. **Kidney:** enhance of Ca excretion from urine.

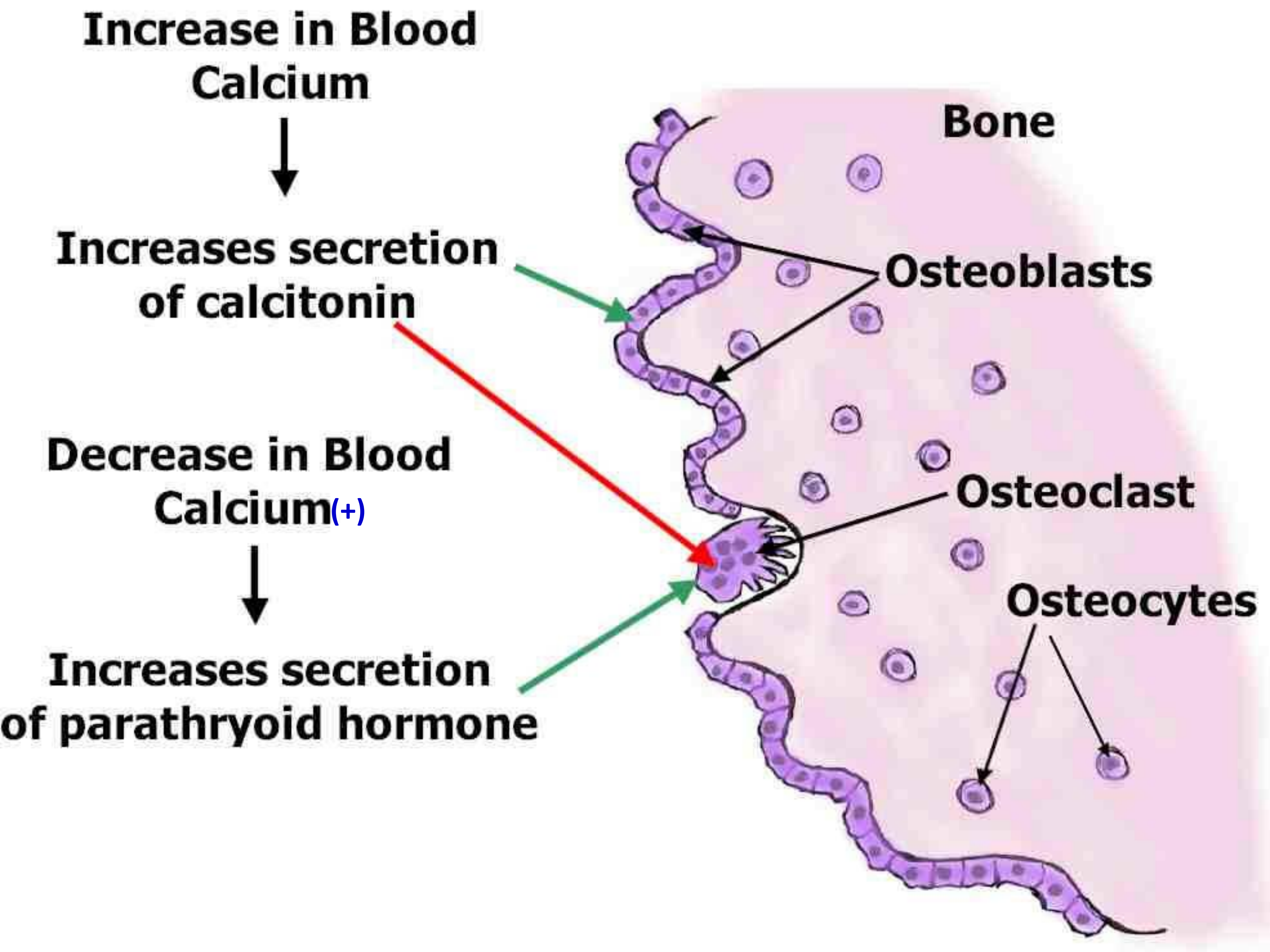
- **PTH and Calcitonin** are **antagonistic in actions**.
- **OR**
- Action of Calcitonin is opposite to that of PTH.

Hormonal Regulators

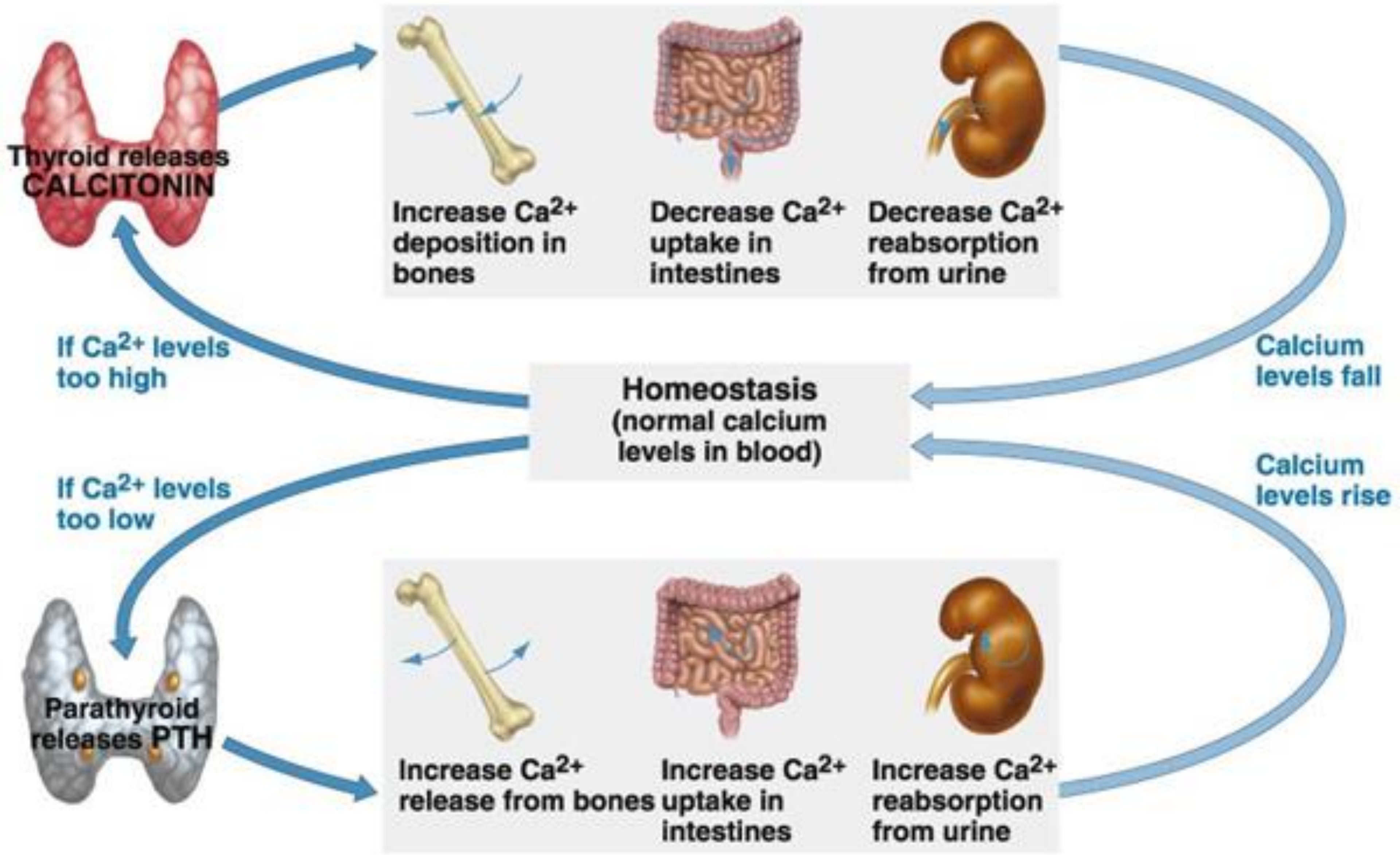
- **Calcitonin (CT)**
  - Lowers Ca++ in the blood
  - Stimulates Osteoblasts
  - Inhibits Osteoclasts

- **Parathormone (PTH)**
  - Increases Ca++ in the blood
  - Stimulates Osteoclasts

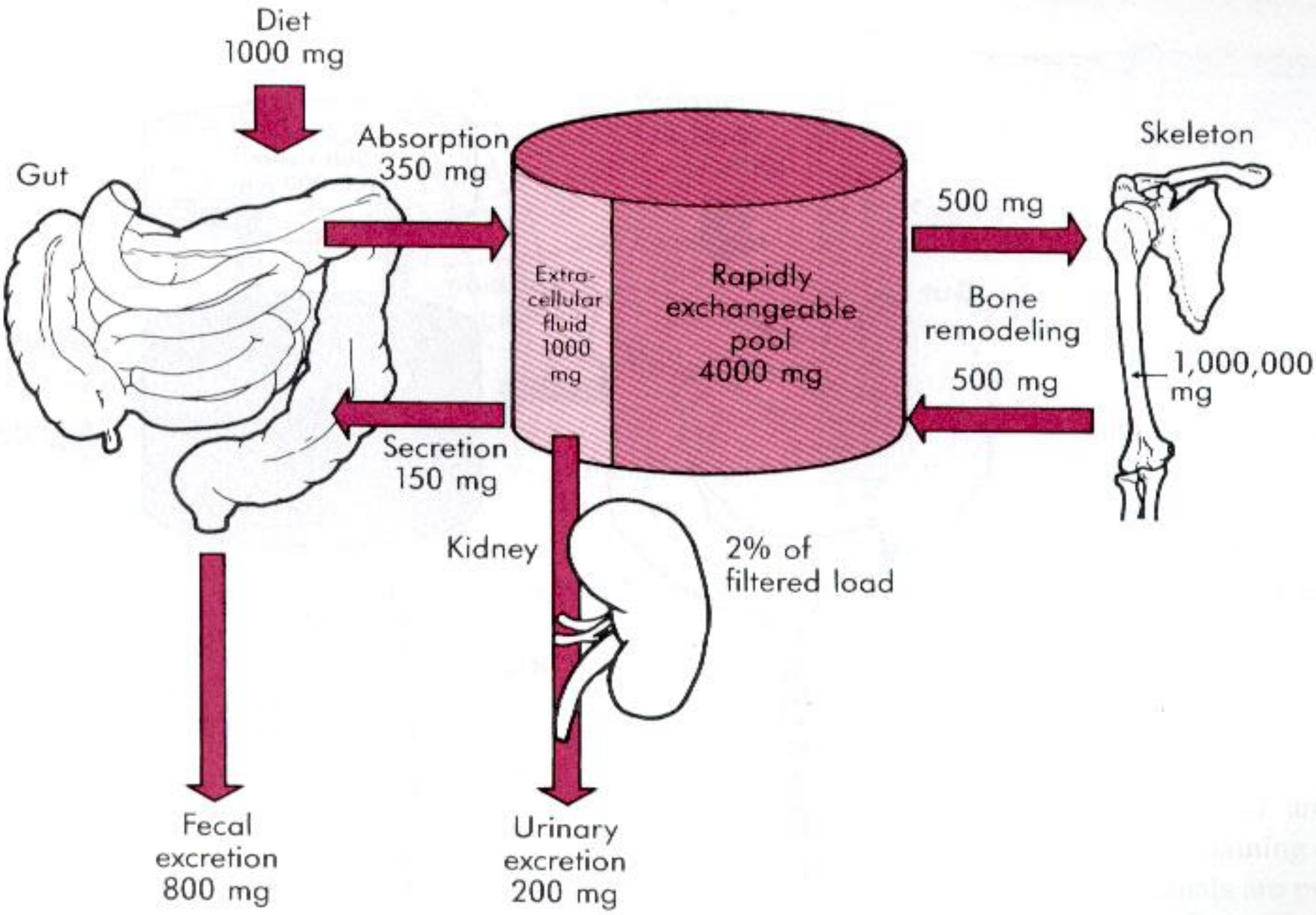
- **Calcitriol**
  - Increases Ca^{++} in the blood
  - Increase Ca^{++} uptake from the gut
  - Stimulates osteoclasts


Increase in Blood Calcium
Increases secretion of calcitonin
Decrease in Blood Calcium(+)
Increases secretion of parathryoid hormone
Bone
Osteoblasts
Osteoclast
Osteocytes

Regulation of Calcium Homeostasis



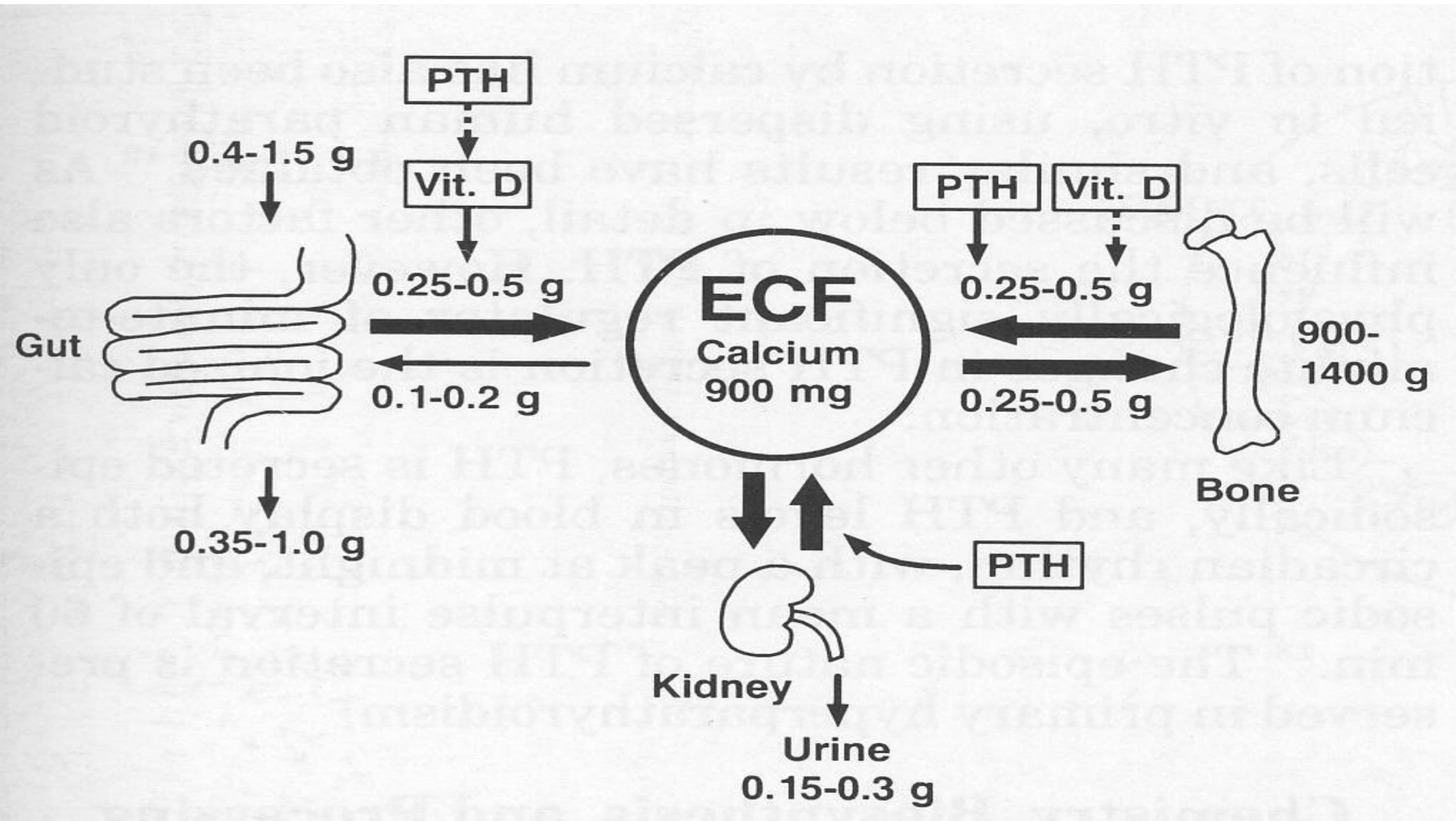
Calcium Turnover



Calcium Balance

- **Calcium Intake = Calcium output**
- **Negative calcium balance**: Output > intake
  - Negative Ca^{2+} balance leads to osteoporosis
- **Positive calcium balance**: Intake > output
  - Positive Ca balance occurs during growth

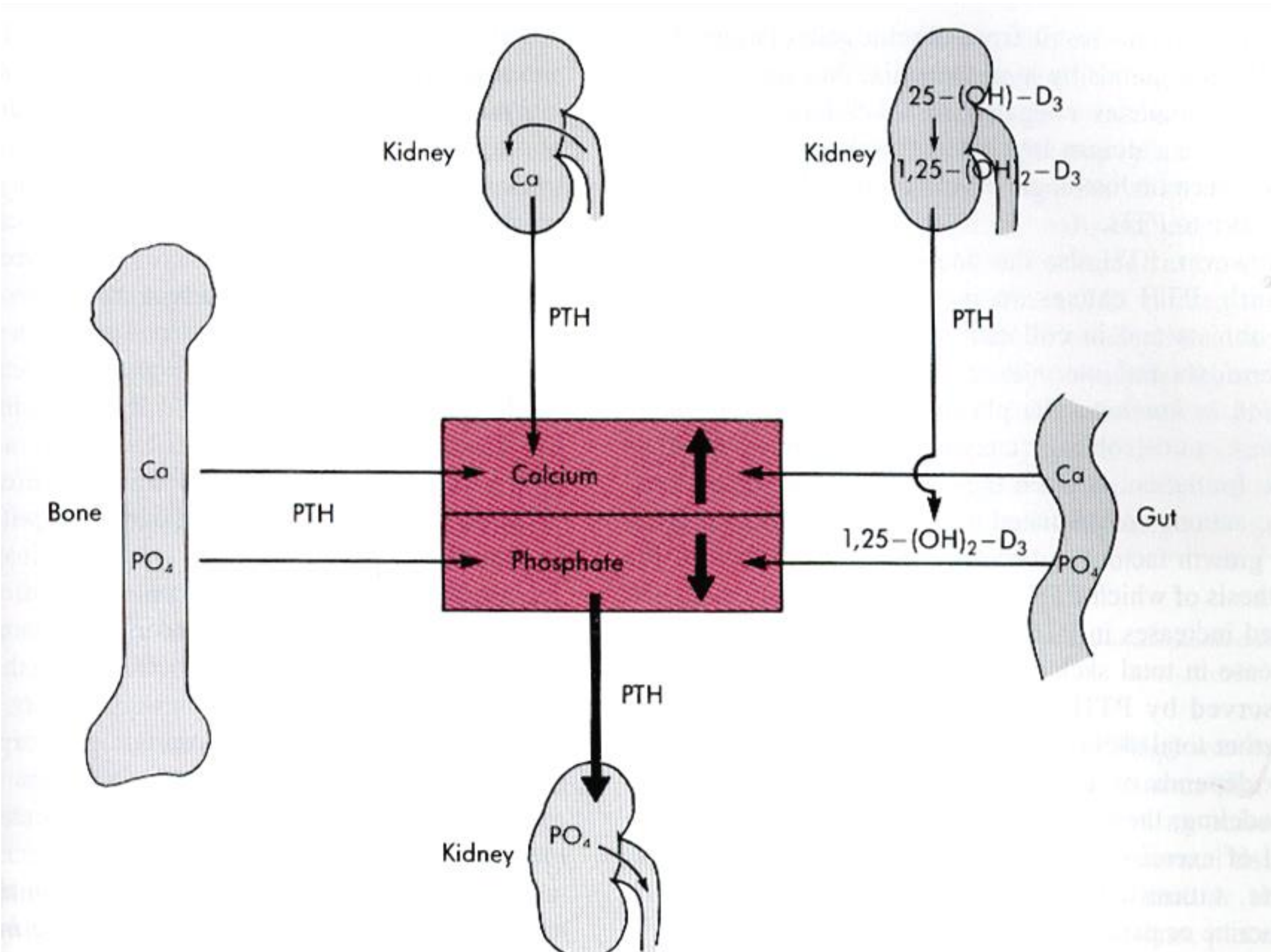
Calcium Balance



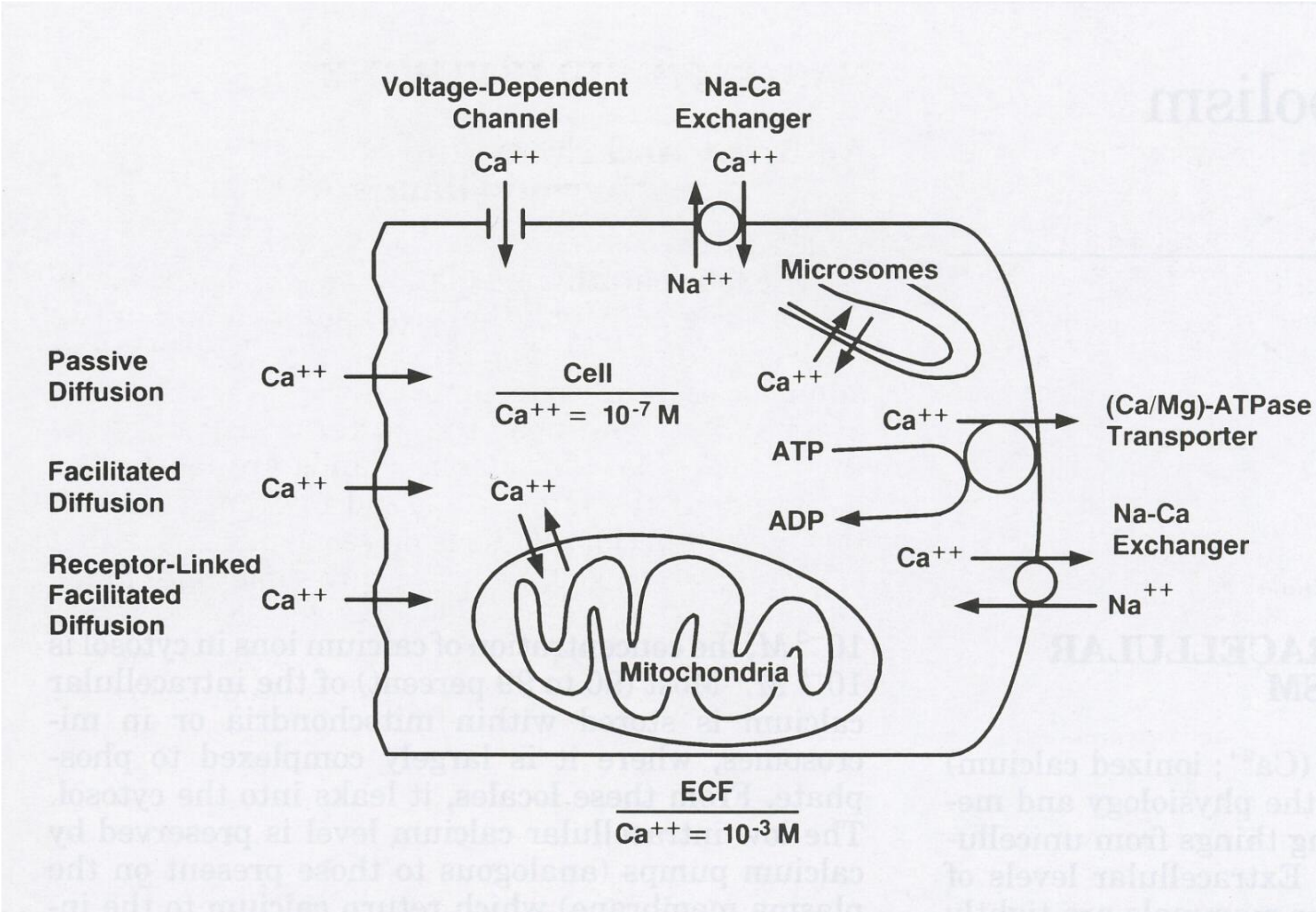
Exercise and Calcium

- Normal bone function requires weight-bearing exercise
- Total bed-rest causes bone loss and negative calcium balance.

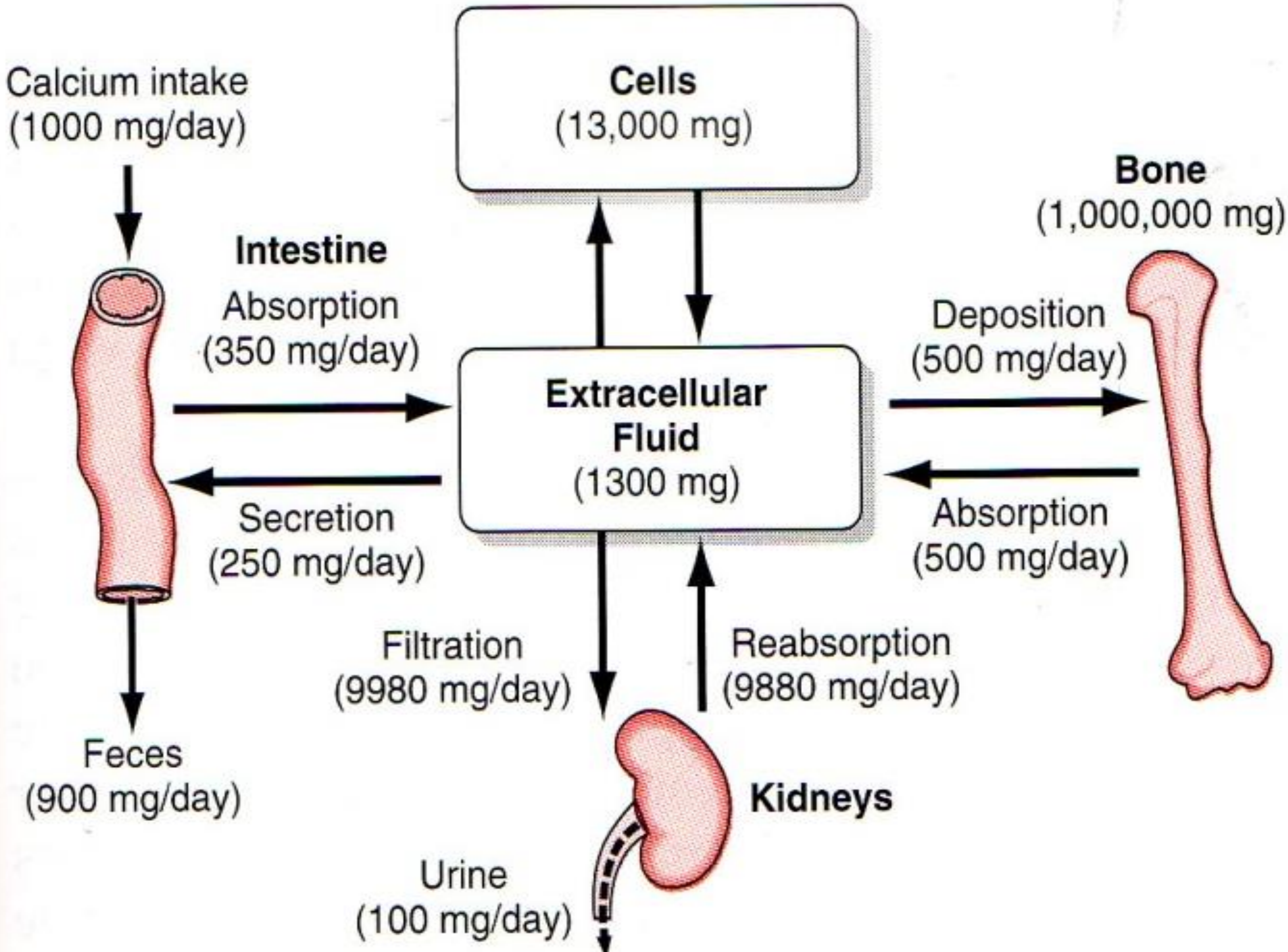
Calcium Homeostasis

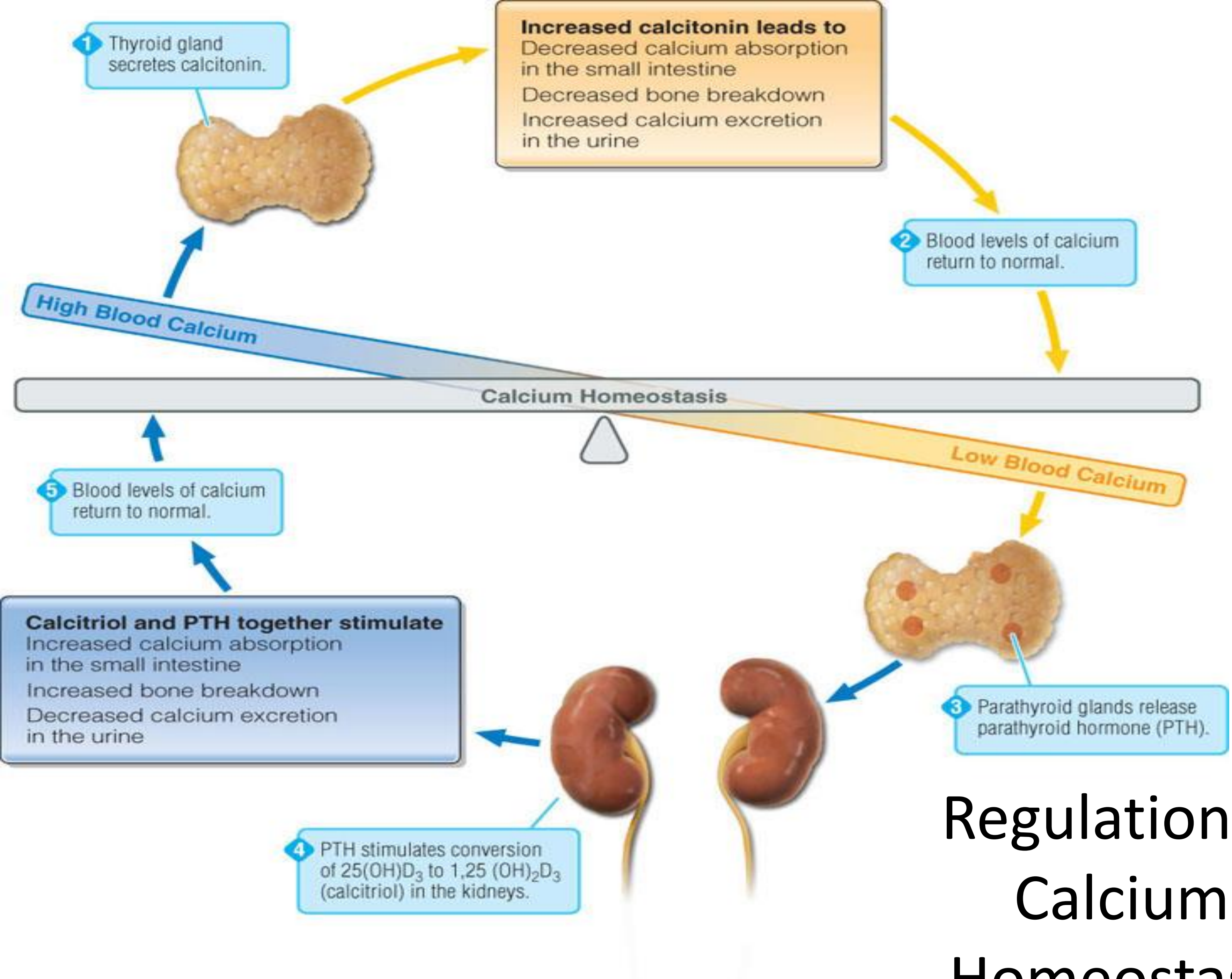


Calcium and the Cell



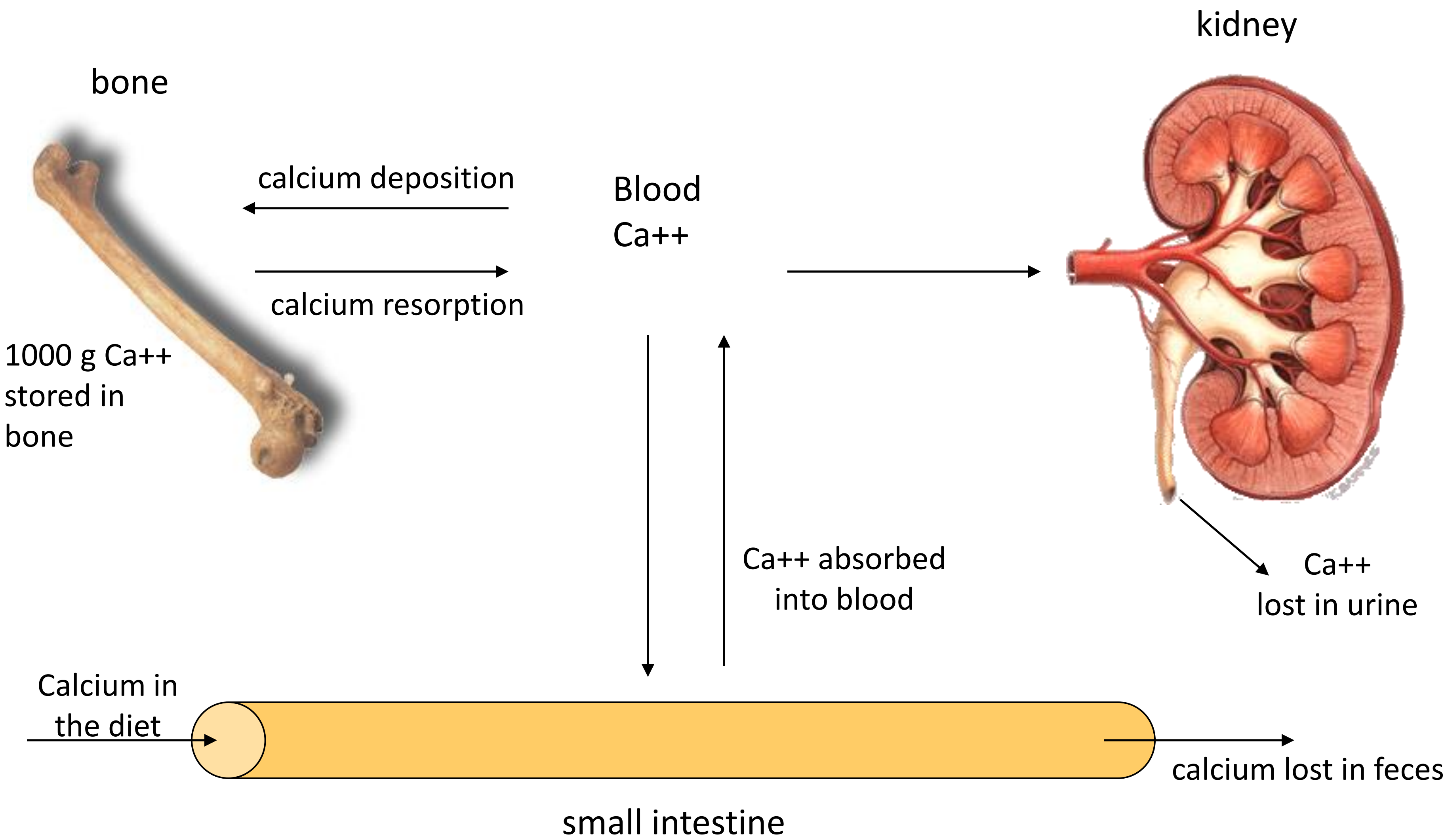
- Translocation across the plasma membrane
- Translocation across the ER and mitochondrion; Ca^{2+} ATPase in ER and plasma membrane


Calcium intake
(1000 mg/day)
Cells
(13,000 mg)
Bone
(1,000,000 mg)
Intestine
Absorption
(350 mg/day)
Deposition
(500 mg/day)
Extracellular
Fluid
(1300 mg)
Secretion
(250 mg/day)
Absorption
(500 mg/day)
Filtration
(9980 mg/day)
Reabsorption
(9880 mg/day)
Feces
(900 mg/day)
Kidneys
Urine
(100 mg/day)

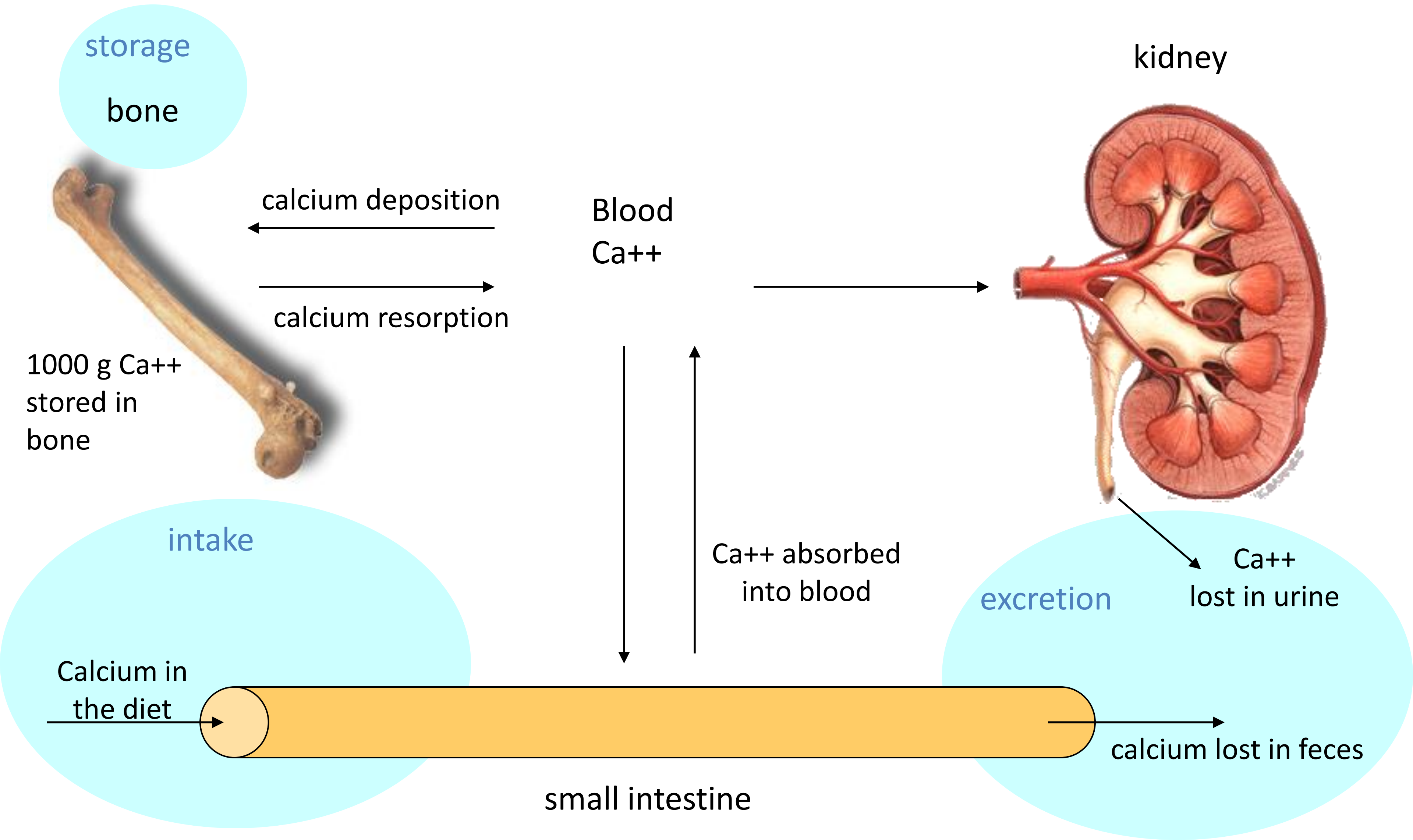


Regulation of Calcium Homeostasis

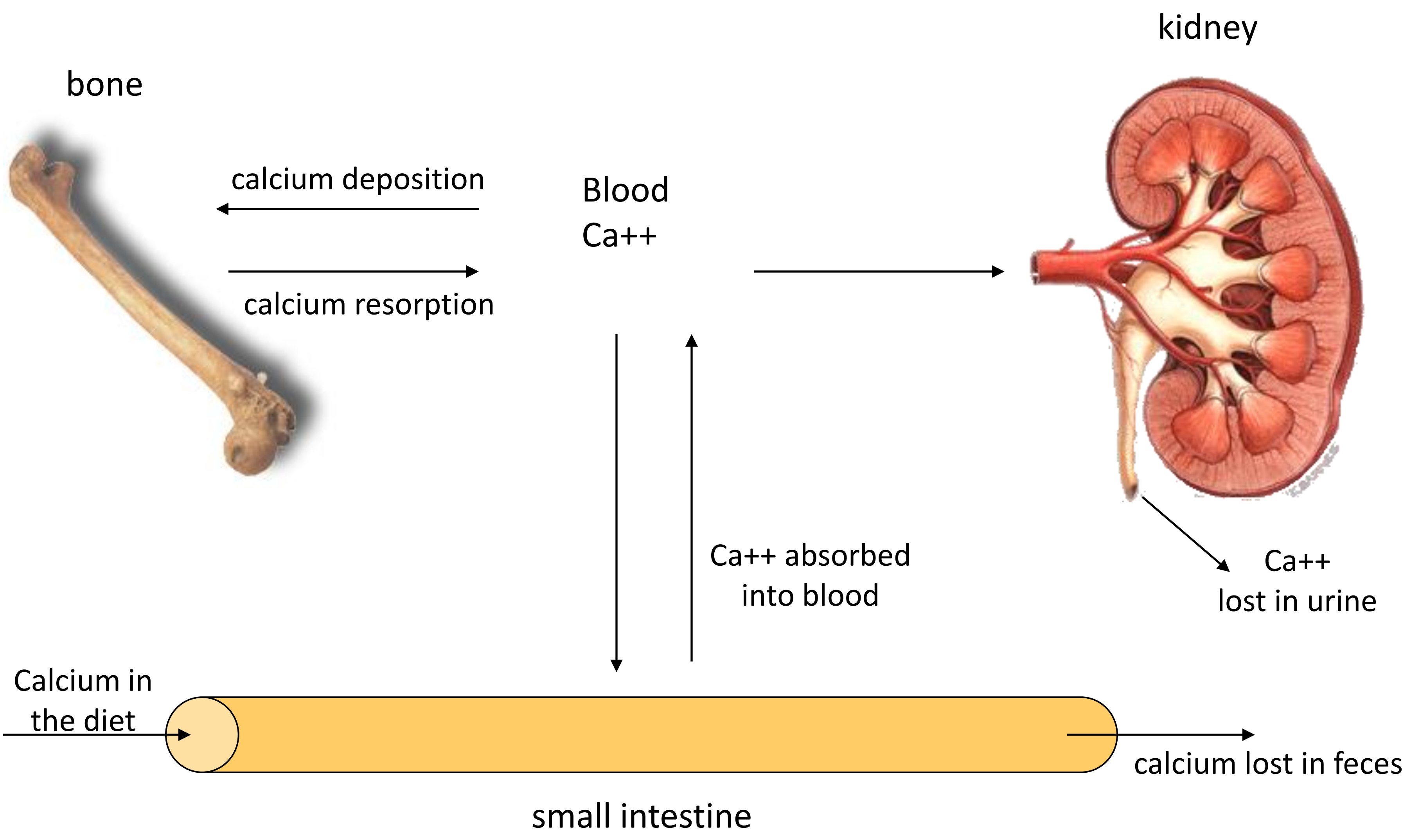
Calcium Homeostasis



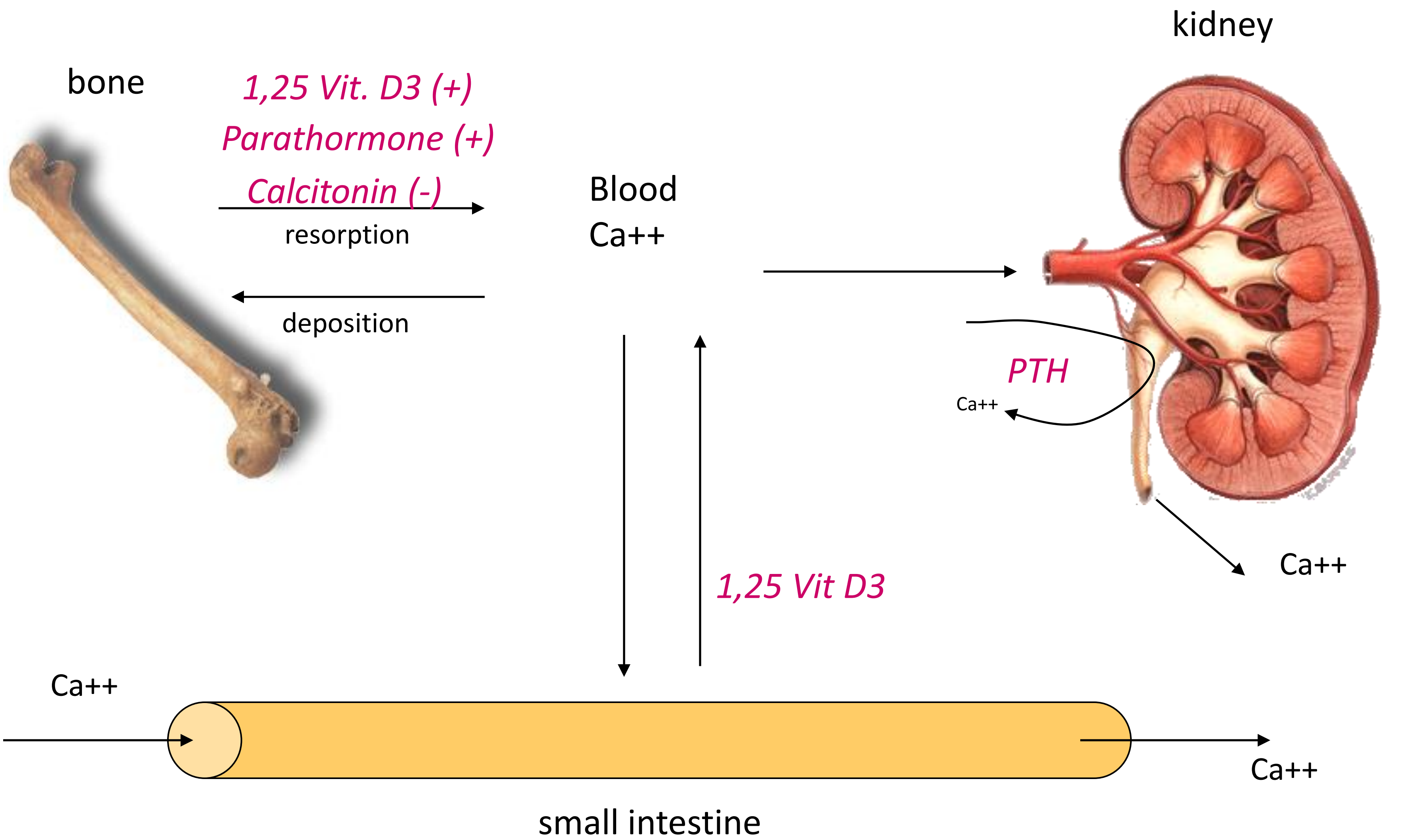
Calcium Homeostasis



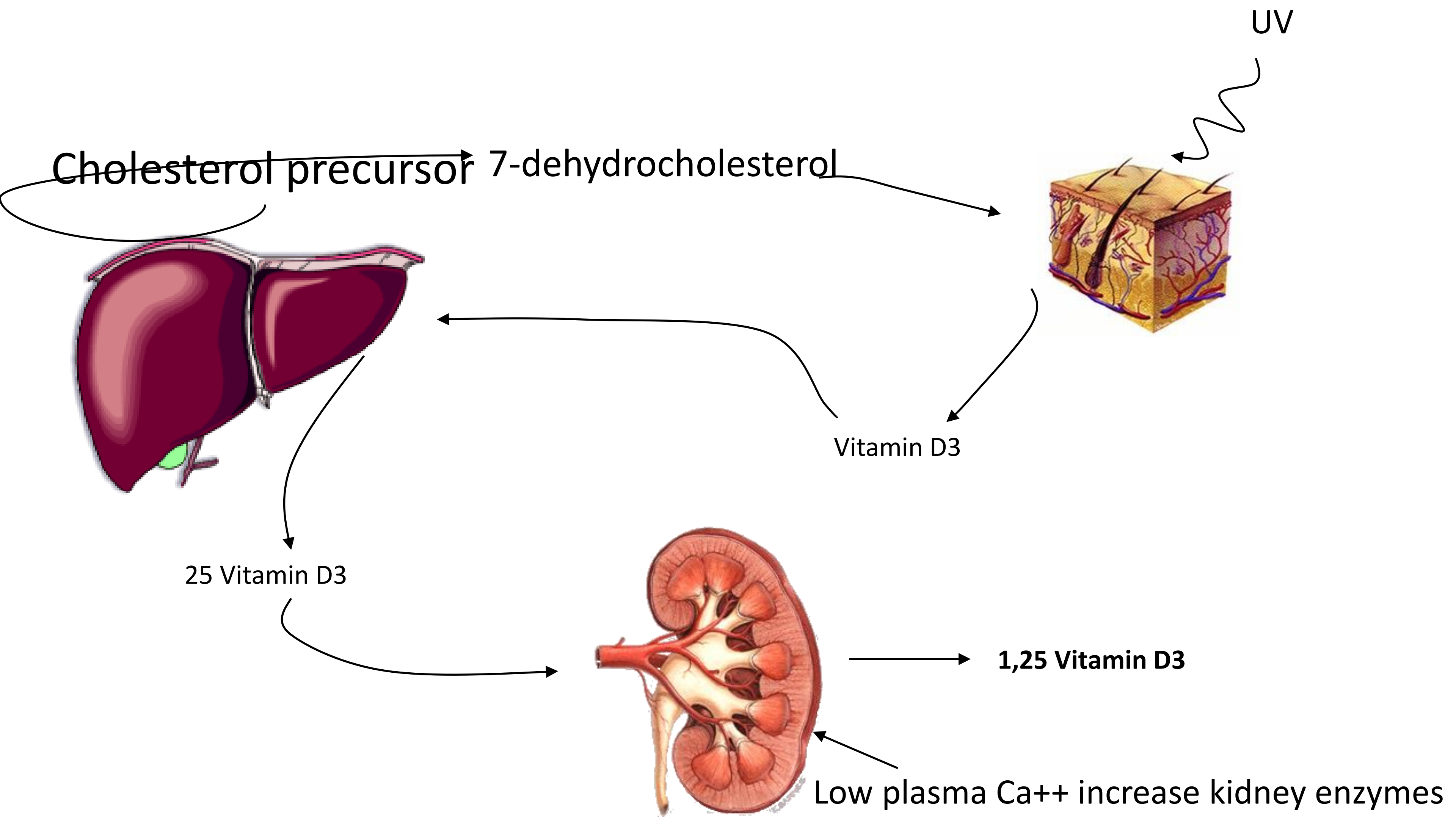
Calcium Homeostasis



Calcium Homeostasis



1,25 Vitamin D3



Excretion Of Calcium

Excretion of Ca

- Mostly through the **intestine**.
- Partly through the **kidney**.

Calcium Excretion

- ❑ In feces: 80%
- ❑ In urine: 20%

- **Unabsorbed dietary Calcium** is mostly **excreted out through feces.**

- Excretion of Ca into the feces is a continuous process
- This is **increased in vitamin D deficiency**

When Will Calcium Excreted In Urine?

- The **renal threshold for Calcium is 10 mg%.**
- When **blood Calcium crosses more than 10 mg% it is excreted in Urine.**

Excretion of Calcium under influence of PTH.

- The excretion of Calcium and Phosphorous is **reciprocally regulated.**
- If **Phosphorous excretion is increased Calcium excretion is decreased.**

• Conditions Increasing Excretion Calcium

- Low Parathyroid hormone (PTH)
- High extracellular fluid volume
- High blood pressure
- Low plasma Phosphate
- Metabolic Alkalosis

- **Excretion Of Calcium Is decreased by:**

- High Parathyroid hormone
- Low extracellular fluid volume
- Low blood pressure
- High plasma phosphate
- Metabolic acidosis
- Low Vitamin D_3

Clinical Significance Of Calcium

Disorders Associated
To
Calcium Metabolism

Defect In Following Factors Leads to Calcium Related Disorders

- **Dietary Intake Of Calcium**
- Role of **PTH , Calcitriol and Calcitonin**
- **Status of Parathyroid , Thyroid , Liver and Kidney**

Investigations To Diagnose Calcium Related Disorders

- Serum Ca and Pi levels
- PTH
- Vit D (1,25 Dihydroxy levels)
- Mg
- Urinary Ca/ Cr ratio

Disorders Of Calcium Metabolism

Hypercalcemia

And

Hypocalcaemia

Hypercalcemia

- **Hypercalcemia** is the condition where there is
- **Persistent high levels of blood Calcium above 11 mg%.**

Conditions Leading To Hypercalcemia

- Excessive intake of Calcium
- **Hyperparathyroidism- Increased PTH**
- Parathyroid Adenoma
- **Hypervitaminosis D**

- **Pagets Disease**

(Increased Release From Bones)

- **Addisons Disease**

(Decreased Excretion Of Calcium)

- **Bone Tumors**

(Leak of Calcium From Bones)

- **Multiple Myeloma-Leukemia , Polycythemia**
- **Milk Alkali Syndrome**(Calcium+Alkali)

– Excessive use of antacids with phosphate-binding
– Prolonged immobility
– Thiazide diuretics
– Thyrotoxicosis

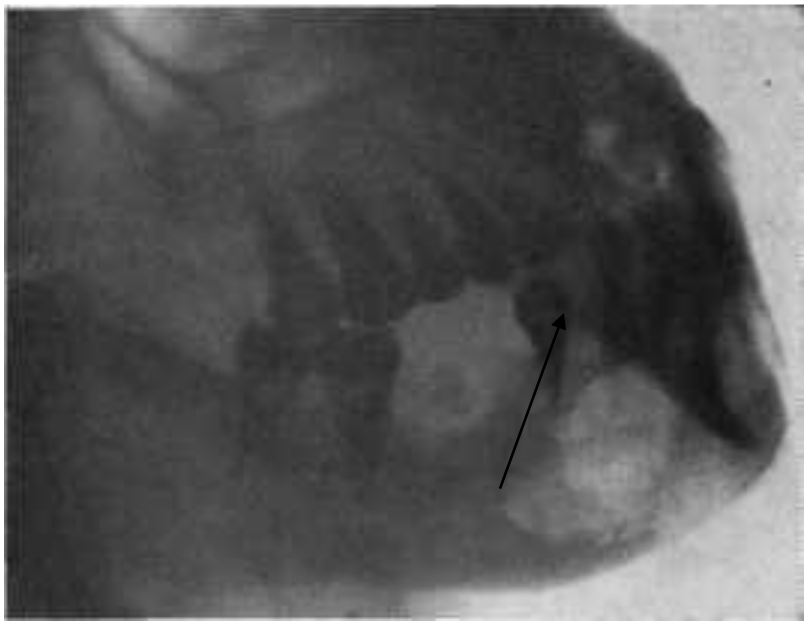
Hypercalcemia Signs and Symptoms

- Muscle weakness
- Personality changes
- Nausea and Vomiting
- Polyuria
- Extreme thirst

- Anorexia
- Constipation
- Pathological fractures
- Calcifications in the skin and Cornea
- Cardiac arrest(prolonged Systole)

Clinical manifestations of Hypercalciemia

Osteodystrophy (Recklinhauzen disease)



Cystosis swelling in the distal ends of both fibula bones

Mechanism

Hyperparatireosis – increasing of Ca in blood – waste of Ca from bones by resorbtion – osteoporosis – overgrowth of connective tissue (but Ca isn't deposited) - osteofibrosis

Hypocalcemia

- **Hypocalcemia** is the condition where there is **persistent low levels of blood Calcium below 9 mg %.**
- Hypocalcemia is **more dangerous and life threatening if not corrected and managed timely.**

Conditions Causing Hypocalcemia

- Malnutrition and Malabsorption
- Diarrhea
- Acute Pancreatitis
- Hypoparathyroidism
- Hypovitaminosis D

- Rickets
- Osteomalacia
- Renal Rickets (Deficiency of 1α Hydroxylase)
- Fanconis Syndrome
- Hypoalbuminemia(Decreases Protein bound Calcium)

- Chronic kidney failure
- Low blood magnesium level (in cases with severe alcoholism)
- Diet high in Phytate

Hypocalcaemia – Clinical Features

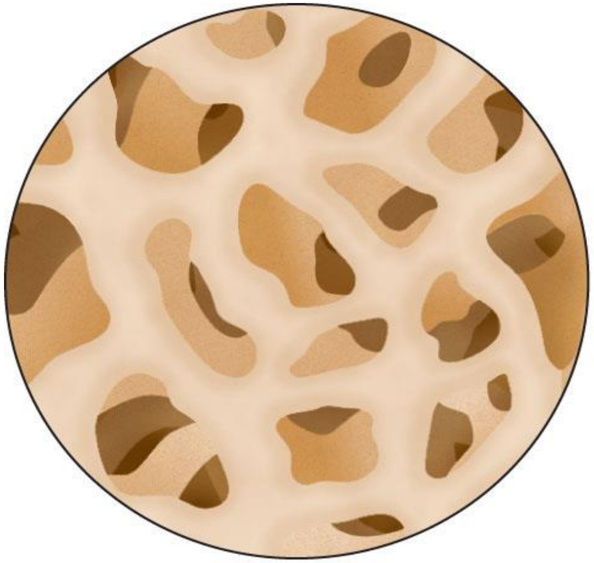
- Neuromuscular excitability
- Paraesthesia (tingling sensation) around mouth, fingers and toes
- Tetany
- Muscle cramps, Carpopedal spasms

- Seizures – focal or generalised
- Laryngospasm, Stridor and apneas (neonates)
- Cardiac Rhythm disturbances (prolonged QT interval)
- Chvostek’s and Trousseau’s signs – latent hypocalcemia

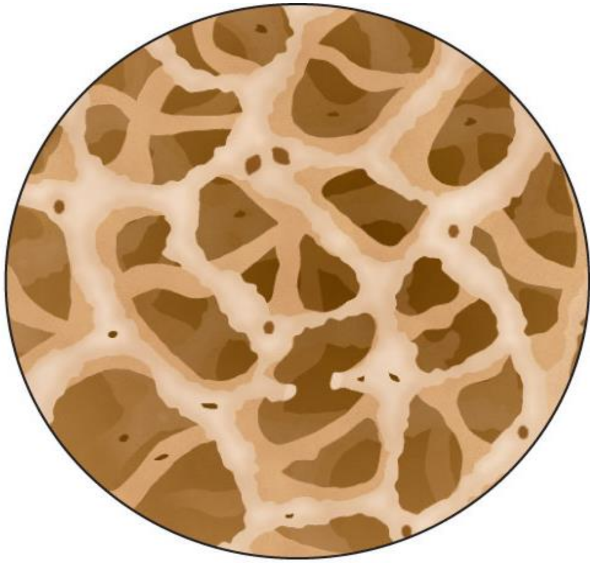
Calcium Deficiency Manifestations

Calcium Deficiencies

- Tetany
- Rickets
  - In growing children's
- Osteomalacia (Osteoporosis)
  - In adult animals



Normal bone



Osteoporotic bone

Tetany

- Tetany is the manifestations caused **due to hypocalcemia.**
- **Serum Calcium below 7 mg % causes Tetany.**

- Tetany is a **life threatening condition.**
- Tetany may be **suffered in persons whom**
  - **Parathyroid gland is surgically removed**
  - **Parathyroid dysfunction due to auto immune disorder**.

- Low Calcium levels **directly affects neuromuscular activity**.
- Leads to **increased neuromuscular irritability of muscles.**

- Twitching and spasm of **muscles of face,hand,feet neck**
- **Carpopedal and Laryngeal and Stridor Spasm.**

Clinical Sign Of Tetany

- **Chvostek's Sign** (Tapping over facial nerve causes facial contraction)
- **Trousseau Sign** (Inflation of BP Cuff for 3 minutes causes Carpopedal spasm).

ECG Changes In Tetany

- Increased Q-T interval in ECG.

- Low blood Calcium
- Increased Phosphate in blood
- Low urine Calcium and Phosphorous

Treatment Of Tetany

- Intravenous infusions of Calcium salts.

Clinical manifestations of Hypocalcaemia

Tetany

The process of tetany potentiation
at the motor neurons and interneuron of spinal cord violate

↓

Conduction of impulses at reflex arch become easier

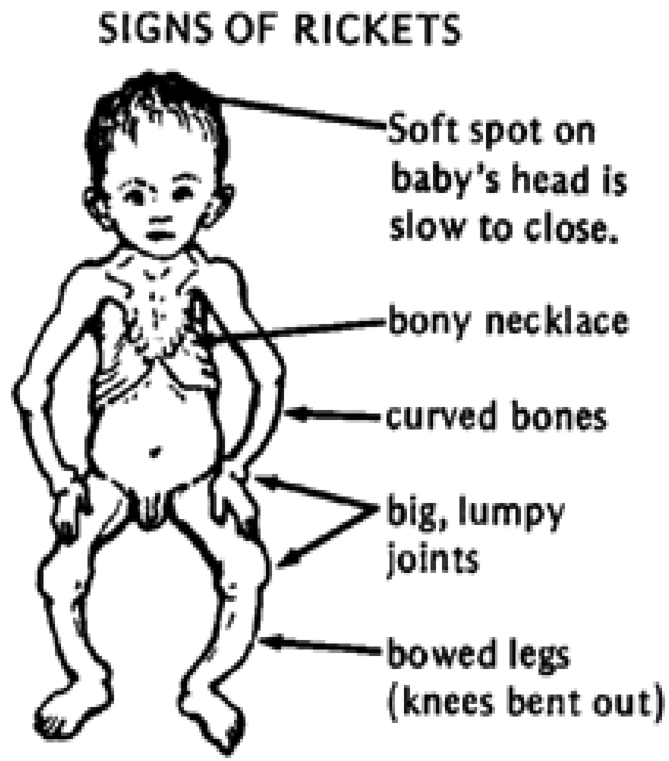
↓

Activate a reflex muscles contraction on mechanical and other stimuli

↓

- Spasm of larynx, bronchus → asphyxia → death
- Cramps
- Coronarospasm (cardiotetanus) → angina → Stop of heart

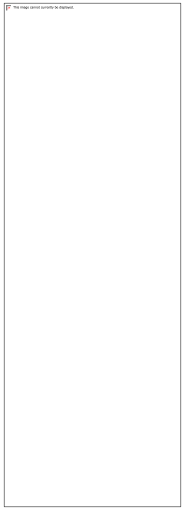
Calcium Deficiencies -Rickets

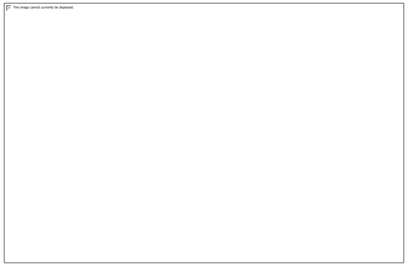


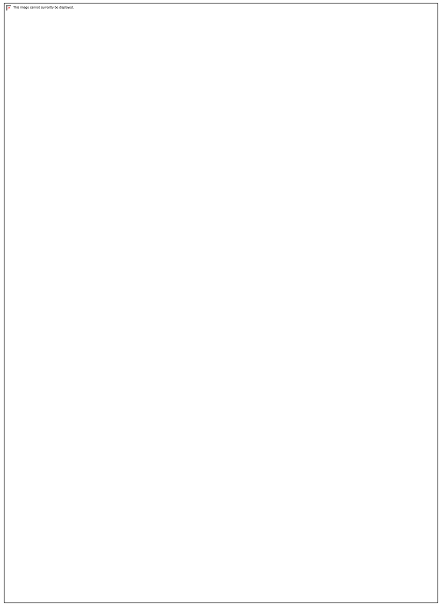
➢weakness and deformity of the bones that occurs from vitamin D deficiency or dietary deficiency of Ca and P in a growing person or animal.

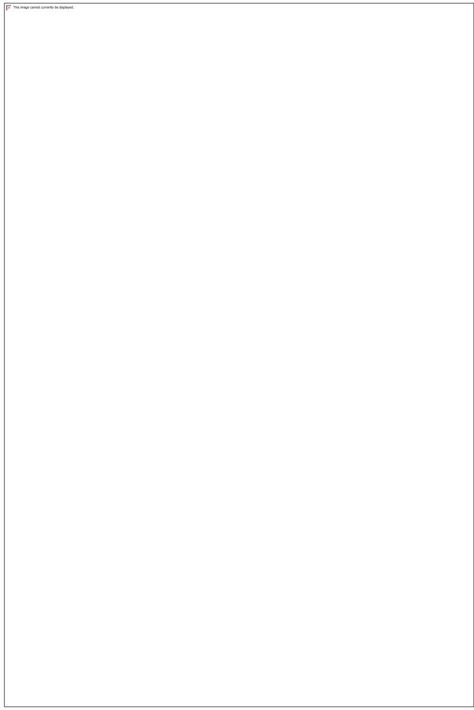
Clinical manifestations of Hypocalcaemia

Ricket



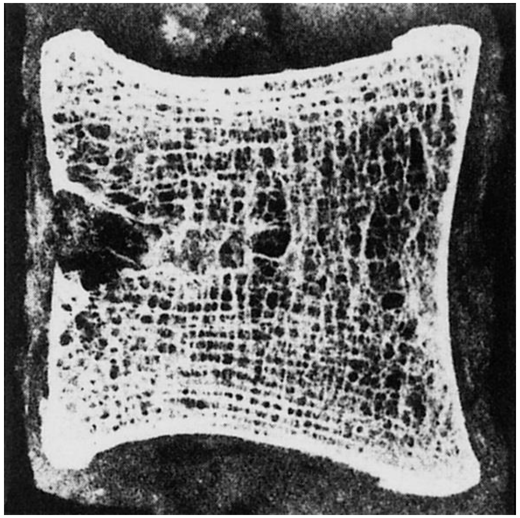


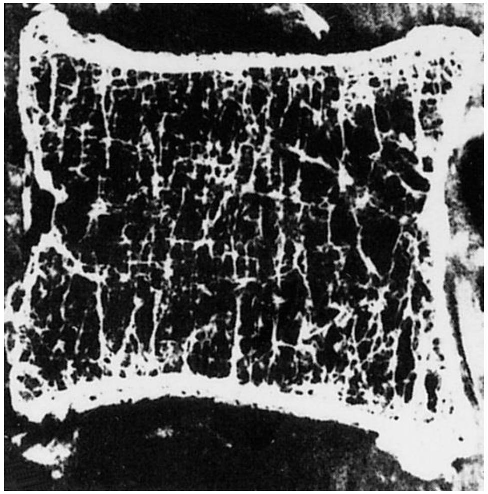


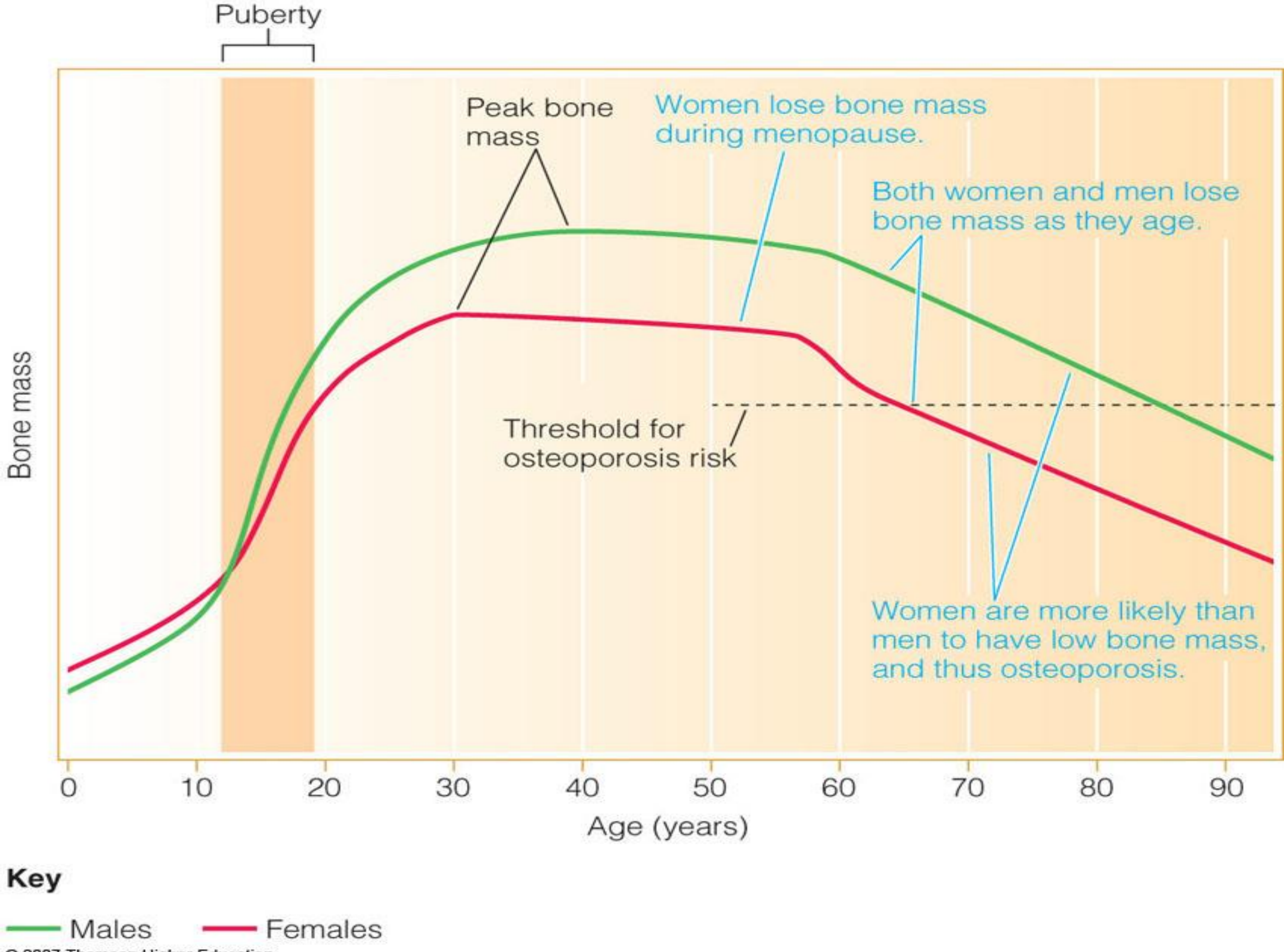


Calcium and Osteoporosis

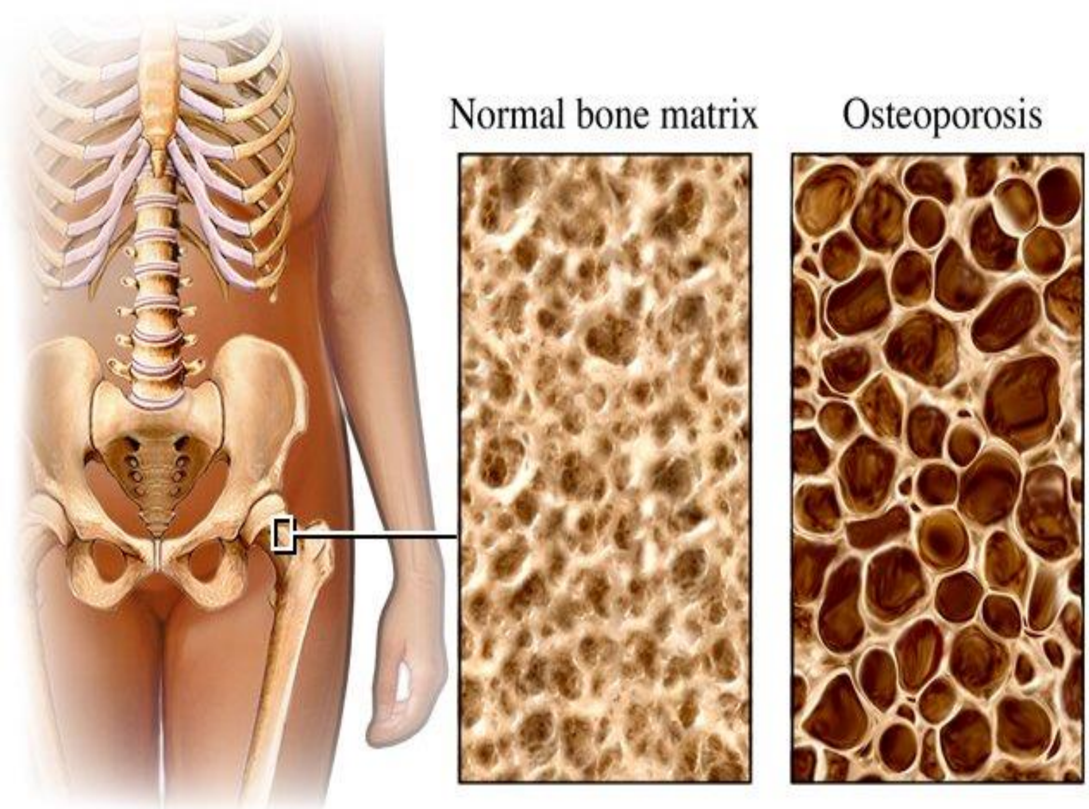
- **Around age 40**, bone breakdown exceeds formation.
- **By age 65, some** women have lost 50% of bone mass.

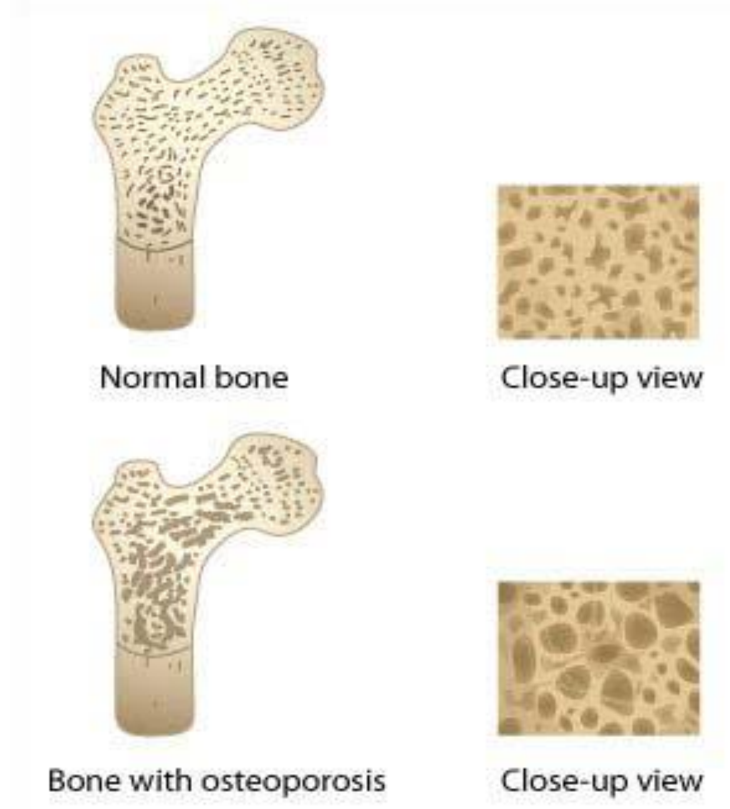





Puberty
Peak bone mass
Women lose bone mass during menopause.
Both women and men lose bone mass as they age.
Threshold for osteoporosis risk
Women are more likely than men to have low bone mass, and thus osteoporosis.
Bone mass
0
10
20
30
40
50
60
70
80
90
Age (years)
Key
Males
Females

Calcium Deficiencies -Osteoporosis

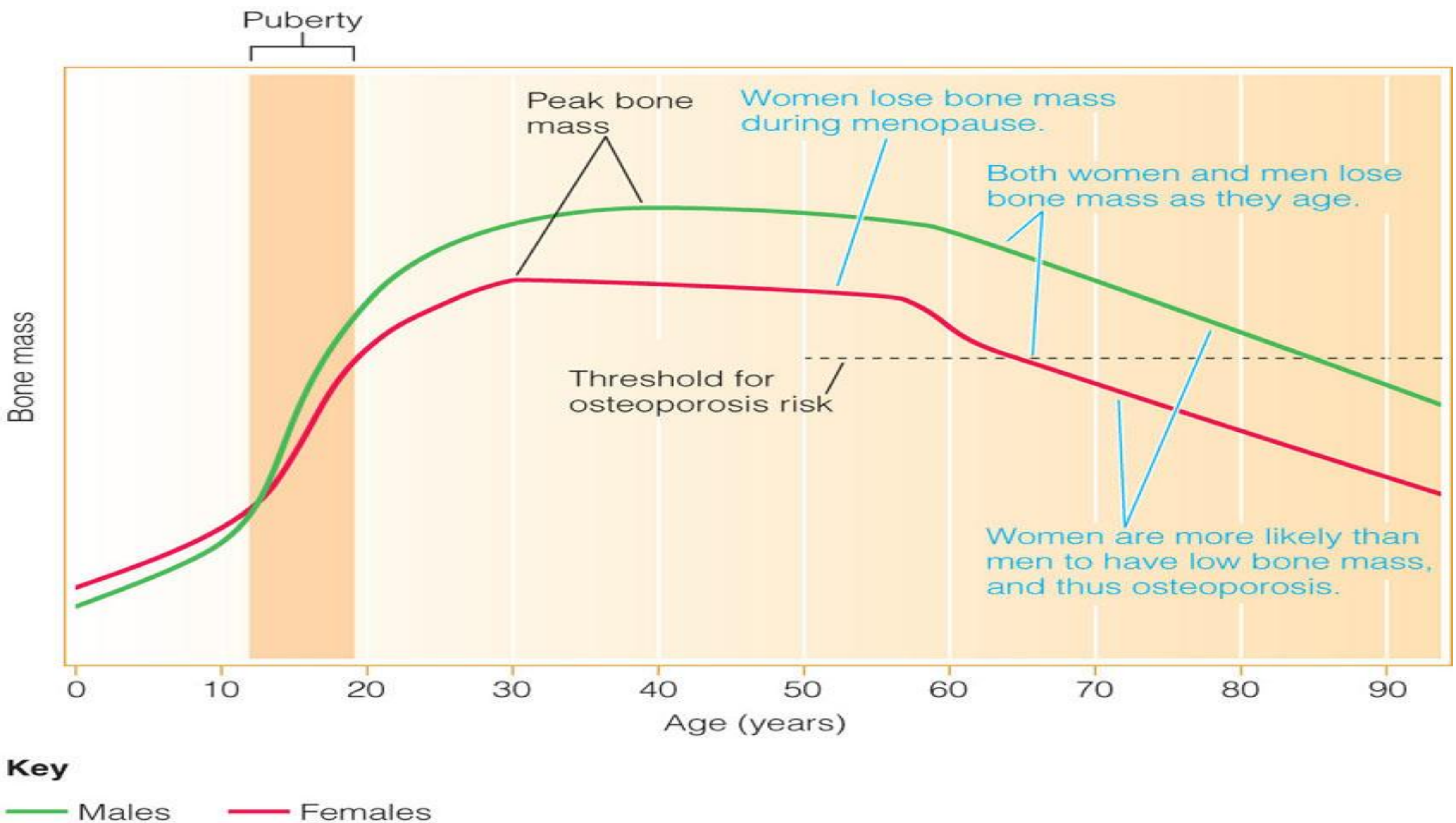




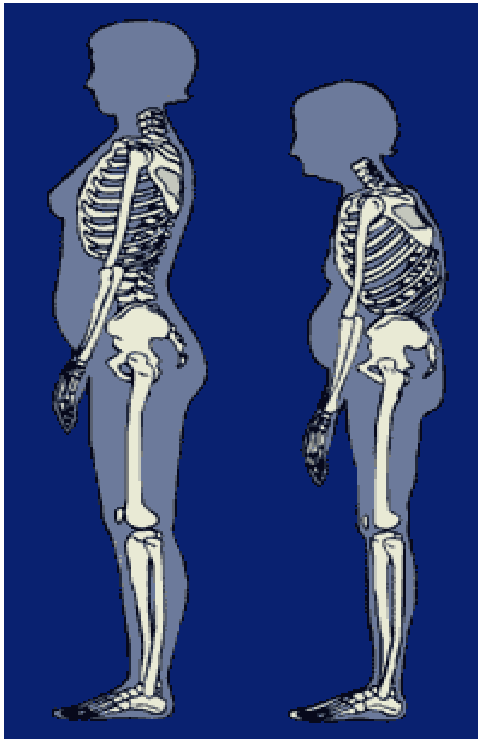
- **progressive loss of bone density, thinning of bone tissue and increased vulnerability to fractures in the elderly people of both sexes.**

Calcium and Osteoporosis

- Bone growth is greatest during "linear growth"
  - Peaks out at around age 30



How does Osteoporosis Look?



Effect Of pH On Extracellular Calcium

- **Binding of Calcium** to **Albumin** is **pH dependent**

- **Acute alkalosis increases calcium binding to protein** and **decreases ionized calcium**

- Patients who **develop Acute Respiratory Alkalosis**
- Have **increased neural excitability and are prone to seizures**
- This is due to:
  - **Low ionized calcium in the extracellular fluid**
  - **Increased permeability to Sodium ions**

Prevention is the Key

- Maintain adequate Calcium and Vitamin D intake—
- Perform weight-bearing exercise
- Take Estrogen supplements?

Treatment of Hypocalcaemia

Severe Symptomatic:

- **IV 10% Calcium Gluconate** @ 0.11 mmol/kg (0.5 mls/kg – max 20 mls) over 10 minutes
- **Continuous IV infusion of Calcium Gluconate** @ 0.1 mmol/kg (Max 8.8 mmols) over 24 hours

Severe Asymptomatic:

Oral Calcium Supplements @ 0.2 mmol/kg (Max 10 mmols or 400 mg Ca) 4 x a day

Calcium Toxicity

- Calcium deposition in soft tissue
- Impaired kidney function
- Interference of other nutrient absorption
  - Iron & zinc

- Toxicity – Hypercalcemia (normally does not to occur)
- Hyperparathyroidism, vitamin D intoxication, cancer are few causes.

Toxicity Of Calcium

- **MAS (Milk Alkali Syndrome)**

- Rare and potentially life threatening condition in individuals **consuming large quantities of calcium and alkali**
- Characterized by **renal impairment, alkalosis and Hypercalcemia**: cause progressive depression of the nervous system

Metabolic calcinosis (інтерстиціальне звапнення)

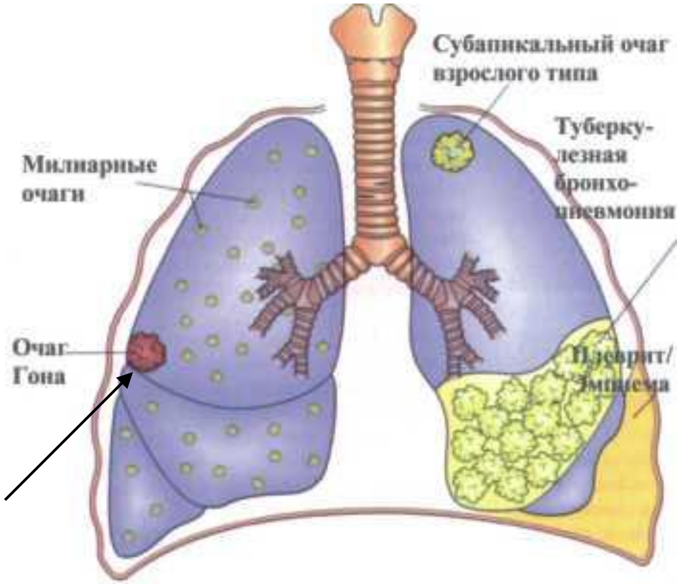
Pathogenesis unknown

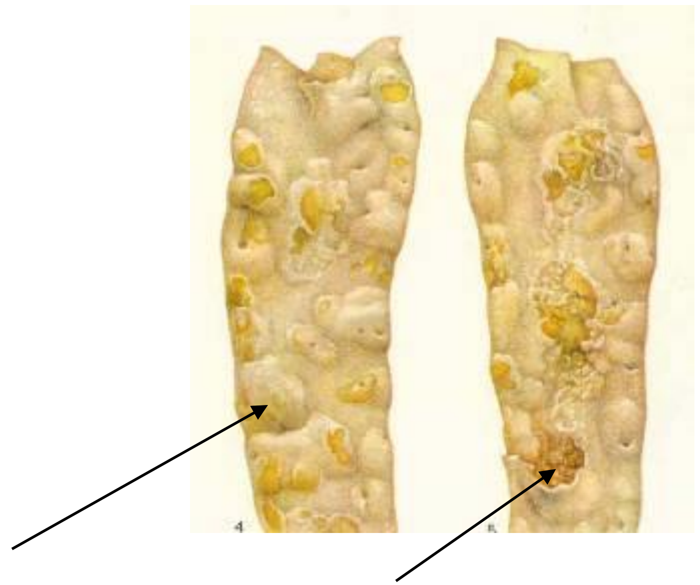
Limestone deposits in skin, tendons, fascias, muscles, along nerves and vessels

Dystrophic static calcinosis (petrification)

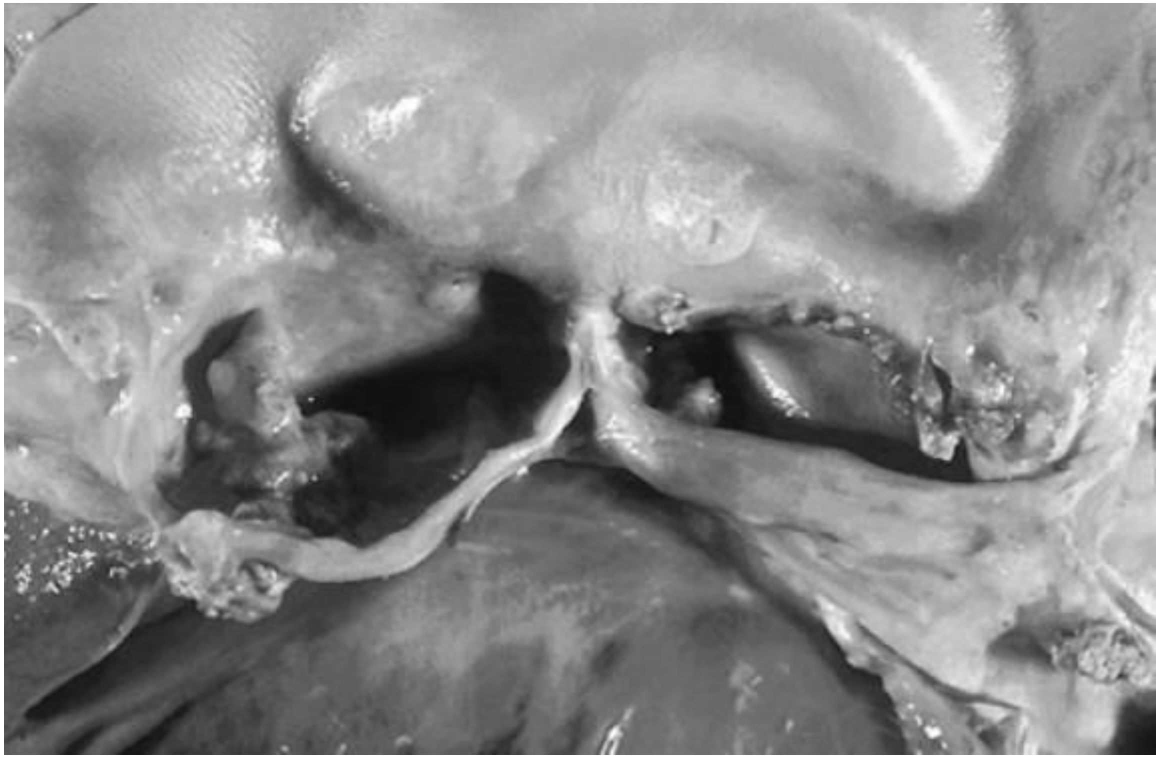
It arises in necrotic and dystrophic tissues - tuberculosis center , infarctions, dead fetus, chronic focus of inflamations (lungs and heart like an armor), focuses of atherosclerosis, scar tissue

Mechanism: alkalinity conditions – increased absorption Ca from blood –
The increased activity of phosphatases, which prodused from necrotic cells – formation of insoluble salts of Ca





Metastasic calcinosis



Calcinosis of aortic valve

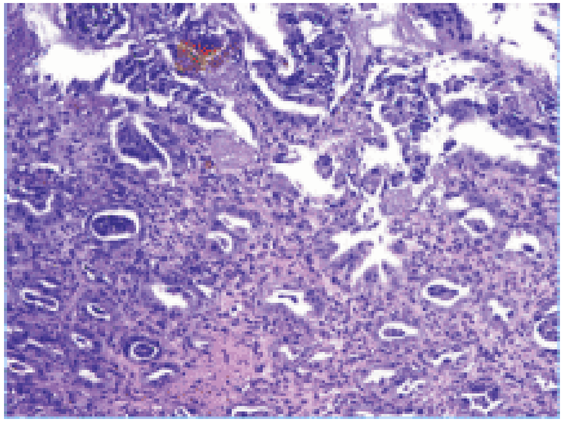


Рис. 5

Кальциноз слизистой оболочки желудка: розоватые кристаллы в собственной пластинке непосредственно под эпителием. Отмечается гиперплазия ямочного эпителия (по A.Srivastava et al., 2007)

Phosphorous Metabolism

Phosphorous

- Phosphorous is a Macromineral /Chief/Principle Element of human body.
- It is a **second most abundant** Mineral of human body.

Daily Requirement/RDA of Phosphorous

- The **dietary Ca:P ratio ideally should be 1:1** for optimal absorption and functions.
- Thus the requirement of **dietary Phosphorous is more or less same as that of Calcium.**

- Adults= 800 mg/day
- Growing Children=1000 mg/day

Dietary Sources Of Phosphorous

- Milk and Milk Products
- Cereals
- Egg
- Meat
- Green Leafy Vegetables , Cabbage , Cauliflower

Absorption Of Dietary Phosphorous

- Absorption of Phosphorous is **along with Calcium**.
- Hence **factors promoting and inhibiting Calcium absorption are likely with Phosphorous**.

- The **Calcium and Phosphorous ratio in diet affects absorption and excretion of Phosphorous.**
- If **any one of this is excess in diet the excretion of the other is increased**.

Body Distribution Of Phosphorous

- **Total content** of Phosphorous in an **adult body is 1 Kg.**
- Phosphorous is **present in each and every cell of body cell.**

- **80 % of Phosphorous** is present in **bones and teeth along with Calcium as Hydroxyapatite crystals**.
- **10% of Phosphorous** is present in **Muscles and blood associated to Proteins, Lipids and Carbohydrate moieties.**

- 10 % of Phosphorous is component of various **Phosphorylated biomolecules**.

Phosphorous In Blood

- In blood Phosphorous is present in following forms:
- **Free/Ionized Phosphorous: 40%**
  - $H_2PO_4^-$
  - HPO_4^{--}

- Bound/Complex forms of Phosphorous:
- Phosphorous bound and present as organic forms- **Non diffusible form.**
- Phosphorous bound to other Cations /Inorganic salt : Calcium Phosphate

- Total Phosphorous levels in Whole blood= 40 mg%
- Serum Inorganic Phosphorous
- Adults= 2-4 mg%
- Children's= 4- 6 mg%

- **Fasting levels of serum inorganic Phosphorous** are **higher than post prandial values.**
- Since after meals the inorganic Phosphorous from blood are **drawn into cells**
- Where it is **utilized for phosphorylation of Glucose , Fructose and Galactose during metabolism**.

- **After a rich Carbohydrate diet** there **decreases serum inorganic Phosphorous levels.**

- In **Diabetes mellitus the levels of serum inorganic Phosphorous get increased due to low utilization** within cells.

Functions Of Phosphorous

- Phosphorous along with Calcium has important role **in bone mineralization and bone development.**

- Phosphorous and Calcium are **components of Hydroxyapatite crystals of bone inorganic matrix**.

- Phosphorous is important component during biosynthesis of certain **Phosphorylated biomolecules viz**:
  - **Phospholipids**
  - **Nucleotides- Components of DNA and RNA**
  - **Phosphoproteins**

- Phosphorylation reactions of metabolism and forming **Esters** ex Glucose-6-PO4,Fru-6-PO4 etc
- **High energy phosphorylated compounds.**
  - Creatine Phosphate ATP,GTP ,CTP ,UTP.
- **Nucleotide Coenzymes** :NAD+,NADP,FAD,PLP

- Phosphorous is a component of **Phosphate Buffer system** which participate in Acid Base Balance.
  - **KH_2PO_4/K_2HPO_4**
- Phosphorous is involved in **phosphorylation of certain enzymes** and bringing **covalent modification.**

Excretion Of Phosphorous

- About **500 mg of Phosphorous** is **excreted through urine per day**.
- **Renal threshold for Phosphorous is 2 mg%.**

- **PTH hormone stimulates the excretion of Phosphorous**

- By **inhibiting tubular renal reabsorption of Phosphorous**.

- Thus there **is inverse relationship of PTH activity and serum Phosphorous levels**.

- **Hyperparathyroidism decreases serum inorganic Phosphorous levels.**

- **Excretion of Phosphorous and Calcium is reciprocally regulated.**

- When **Phosphorous is excreted Calcium is retained and vice a versa.**

Disorders Associated To Phosphorous

Hyperphosphatemia

- **Hyperphosphatemia** is **abnormally persistent high levels**
- **Of serum Inorganic Phosphorous above the normal range**.

Conditions Causing Hyperphosphatemia

- Increased dietary intake of Phosphorous
- **Hypoparathyroidism**

 (Decreased PTH decreased excretion)
- **Hypervitaminosis D**

 (Increased Calcitriol increased absorption)

- Bone Tumors

(More turn over of Phosphorous)

- Diabetes mellitus

(Decreased utilization)

- Renal Failure
- Chronic Nephritis
- Intake of Steroids

(Decreased excretion)

Hypophosphatemia

- Hypophosphatemia is **abnormally persistent low levels**
- Of **serum Inorganic Phosphorous below the normal range.**

Conditions Of Hypophosphatemia

- Starvation and Malabsorption Syndrome
- Hyperparathyroidism
- Hypovitaminosis D
- Rickets
- Osteomalacia
- Rich Carbohydrate diet
- Intake of antacids, contraceptives and Diuretics

Sulfur Metabolism

Sulfur

- **Sulfur** is an essential **Macromineral.**
- **Third most abundant** Mineral of human body.

RDA of Dietary Sulfur

- No specific dietary requirement for Sulfur.
- Sulfur as **free element cannot be utilized**.

- **Sulfur is mainly associated** to **Sulfur containing compounds** viz:
  - **Sulfated Amino acids and Proteins**
  - **Sulfolipids**
  - **Mucopolysaccharides (Sulfated)**
  - **Sulfated Vitamin B complex members: Thiamine, Pantothenic acid, Biotin and Lipoic acids**

- **Proteins** contains about **1% Sulfur by weight.**
- The ingestion of dietary Proteins rich in **Sulfur containing amino acids is sufficient source of Sulfur.**

Dietary Sources Of Sulfur

- **Dietary sources of Sulfated Proteins:**
- Egg
- Fish
- Meat
- Liver
- Legumes
- Cereals

Dietary Absorption

- The **sulfated Amino acids** are **absorbed from intestine**
- Through **active transport mechanism**.

Body Distribution Of Sulfur

- The **total content of Sulfur** in an adult body is **150-200 gm.**
- Very **small amount of inorganic Sulphate occurs in tissues** and body fluids.
- **Sulfur levels in blood=0.1-1 mg%**

Functions Of Sulfur

- **Sulfur in the body** is present in **organic form** as various biomolecules carrying following functions:

- **Sulfated Proteins ,Enzymes containing Sulfur containing amino acids** possess –**SH groups serves as functional parts.**

- The **SH groups are responsible for forming S-S bonds in the structures**.

Sulfated Compounds Of Human Body

- Immunoglobulins
- Keratin of Nail and Hair
- Glutathione Peroxidase
- FAS Complex
- Coenzymes-TPP , Biotin ,CoA

PAPS

- Phospho Adenosine Phospho Sulfate(PAPS) is an **active Sulfate**

- **PAPS** is a **conjugating agent** involved in:
  - **Detoxification process**
  - **In Conjugation reaction**
  - **By Sulfuration**

- Substances like **Phenol , Indole , Skatole and Steroids** are detoxified by **Sulfuration Conjugation reaction**

- To form Organic Sulfates like **Etheral Sulfates: Indoxyl Sulfate, Skatoxyl Sulfate to get excreted in urine.**

- **PAPS** is also used during **biosynthesis of Glycosaminoglycans/MPS:**
  - **Heparin**
  - **Chondritin Sulfate**
  - **Dermatan Sulfate**
  - **Keratan Sulfate**

- **SAM** activated **Methionine a Sulfated Amino acid**
- Is an **active donor of Methyl groups**
- SAM is actively involved in **Transmethylation reactions**.

- **Iron Sulfur Proteins** are **components of ETC** (Respiratory Chain).

Excretion Of Sulfur

- The Sulfur from different **sulfated compounds is oxidized in Liver** and **excreted through Urine.**

- **Urine excretes both inorganic and organic forms of Sulfur.**
- In the form of **Thiocynates** and **Sulfur containing amino acid**.

Forms Of Sulfur Excreted

- Inorganic Sulfate = 80%.
- Organic Sulfate/Etheral Sulfate-10 %
- Unoxidized Sulfur =10%

Magnesium Metabolism

Magnesium

- Magnesium (Mg) is a **Macromineral** of human body

- It is the **fourth most** abundant mineral and **important Cation of human body.**

Daily Requirement/RDA of Magnesium

- Adults = **300-400 mg/day**

- **High doses of Mg above 600mg/day orally causes diarrhea.**

Dietary Sources Of Magnesium

- Cereals
- Nuts, Beans , Almonds
- Meat, Milk
- Green Leafy Vegetables (Chlorophyll-Mg)
- Cabbage, Cauliflower
- Fruits

Absorption of Mg

- About **50-80 % of dietary Magnesium** is **absorbed** by intestinal mucosal cells.
- Through a **specific carrier system.**

Factors affecting Mg Absorption

Factors promoting Mg absorption:

- PTH
- Calcitriol

Factors inhibiting Mg absorption:

- High Calcium and Phosphorous in diet
- Phytates
- Fatty acids
- Alcohol consumption

Body Distribution Of Magnesium

- **The content of Mg** in an adult body is **20 gm.**
- **70 % of Mg** is in **bones along with Ca and P**
- **30 % of Mg** is in **soft tissues and body fluids.**

Blood Magnesium Levels

- **Free/Ionized** form of Mg **-60%**
- Mg bound to **Proteins-30%**
- **Salts of Mg-10%**

Normal range of Serum Magnesium- 2-3 mg%

Functions Of Magnesium

- Magnesium **along with Calcium and Phosphorous.**
- Is a **component of inorganic matrix of Bones and Enamel of teeth**

- **Ionized form** of Magnesium has **role in neuro muscular function.**

- Mg^{++} is **inorganic cofactor of Enzyme Kinases:**
  - **Hexokinase**
  - **PFK**
  - **PK**
  - **Glucokinase**

- Mg has role in **sensitizing Insulin**
- **Which Promotes Glucose uptake by cells.**

- Mg is a **component of Chlorophyll pigments of plants.**
- Hence **green leafy vegetables are good sources of Mg.**

Disorders Associated To Magnesium

Hypomagnesemia

- Hypomagnesemia **low levels of Mg(< 2mg%)** leads to :
- **Neuromuscular irritability**
- The manifestations are **managed by oral dosage of Mg^{+2}**

Hypomagnesemia Conditions

- Starvation and Malnutrition
- Malabsorption
- Chronic Alcoholism
- Liver Cirrhosis
- Uncontrolled Diabetes mellitus(Osmotic diuresis)
- Hyperthyroididsm
- Rickets

Hypermagnesemia

- Hypermagnesemia is **increased levels of serum Mg.**

- Hypermagnesemia depresses nerve conduction.

Hypermagnesemia Conditions

- Hypothyroidism
- Advanced Renal Failure (Less excretion)

Sodium Metabolism

Sodium

- Sodium is an **essential Macromineral**
- Sodium serves as a **body Electrolyte.**
- Sodium (Na^+) is the **chief Cation of ECF.**

RDA Of Sodium

- Sodium is taken through diet in the form of NaCl.
- **5-10 gm of NaCl per day** provide the required amount of Na.
- 10 gm of NaCl contains **4 gm of Na.**

Remember

- Hypertensive patients /**Patients having history of Hypertension** should limit their intake of NaCl.
- For them **RDA is 1 gm NaCl/day.**

Dietary Sources of Na

- Common Salt (NaCl)
- Bread
- Whole grains
- Nuts
- Eggs
- Milk
- Green Leafy Vegetables

Absorption Of Sodium

- Sodium is **readily absorbed from GIT.**
- Less than **2 % is normally excreted through feces.**
- However **in diarrhea large quantities of Na is lost through feces.**

Body Distribution Of Sodium

- 50% of Sodium is in bones
- 40 % of Sodium is in ECF
- 10% of Na is in Soft tissues.

- **Na^+ is estimated by Electrolyte Analyzers**
- Normally in Serum Na^+ - **136-146 mEq/L.**
- Na^+ in **ICF is 35 mEq/L**

Biomedical Functions Of Na

- Na^+ along with other electrolytes in ECF **exerts osmotic pressure and maintains fluid balance**.

- Na^+ has role in **neuromuscular function.**

- Na is a component of **ECF buffer system** **plays role in acid base balance.**

- Na^+ is involved in **Sodium dependent active transport mechanism**
- For **Glucose , Galactose and Amino acids absorption** from GIT lumen into the intestinal mucosal cells.

- Sodium has role in **maintenance of cell permeability.**
- Sodium **initiates and maintains heart beat** .
- Hence high **Sodium content in hypertensives aggravate the condition of BP.**

Excretion Of Sodium

- Sodium absorbed from GIT after its functional role it is excreted out through Urine.
- Sodium metabolism is **influenced** by **Aldosterone a Mineralocorticoids.**

- **Aldosterone act to:**
  - **Increase renal reabsorption** of Na from ultrafiltrate.
  - **Retain blood Sodium.**
  - **Decrease Na excretion**.

- **In Adrenocortical insufficiency** there is **decreased Aldosterone**

- Which **decreases renal reabsorption of Na** leading to **Hyponatremia**.

- **Na is alternatively excreted out** through **Skin sweating.**

Disorders Of Sodium Metabolism

Hypernatremia

- **Sodium levels above 150 mEq/L** in ECF is termed as Hypernatremia.

Conditions Causing Hypernatremia

- Parenteral Therapy (**IV infusion) with Saline Solution.**

- **High intake of Salt without corresponding in take of Water**

- **Hyperaldosteronism** (Increased renal reabsorption of Na)

- Cushing's Syndrome (Hyper Adrenal Cortex Activity)
- Osmotic diuresis
- Decreased ADH secretion (Causes Hemoconcentration)

Hyponatremia

- Hyponatremia is decreased levels of blood Na .
- **Low Sodium levels is an emergency critical condition** which has to be managed at earliest.

Conditions Causing Hyponatremia

- Diarrhea
- Excessive Sweating
- Nephrotic Syndrome
- Addison's Disease (Decreased Na+ renal reabsorption)
- Malnutrition

Potassium Metabolism

Potassium

- Potassium (K) is a **Macromineral and a body Electrolyte**.
- K+ is a **chief cation of ICF**.

RDA and Dietary Sources Of Potassium

- 3-4 gm/day is the RDA for Potassium.

Dietary Rich Sources Of K^+

- Fruits: **Banana ,Oranges ,Pineapple**
- **Tender Coconut water**
- Potatoes
- Beans
- Chicken,Liver

Absorption Of Potassium

- **90% of K is efficiently absorbed** from GIT and **very little is lost through feces.**

- During **diarrhea there is significant loss of K+ ions** out from the body.

Blood Levels Of Potassium

- **Whole blood** contains K^+ level upto = **50 mEq/L**
- K^+ is the chief Cation of ICF
- The **serum /plasma K^+** is **3.5-5.0mEq/L**

Biochemical Functions Of Potassium

- Potassium along with other blood **Electrolytes**
- **Exerts Osmotic pressure and maintains fluid balance in E.C.F and I.C.F.**

- K^+ has role in **neuromuscular function.**
- K^+ of E.C.F influences **Cardiac muscle activity.**

- **K^+** is component of **I.C.F buffer system**
- **Plays important role in acid base balance.**

- K^+ is **cofactor for Enzyme Pyruvate Kinase of Glycolysis.**

- K+ of I.C.F is necessary for **proper Protein biosynthesis by Ribosomes.**

Excretion Of Potassium

Excretion of **Na^+ and K^+ are reciprocally regulated.**

- If **Na^+ is excreted** K^+ is **retained** vice a versa.

- **Aldosterone increases K^+ excretion .**
- Aldosterone **inhibits tubular renal reabsorption** of K^+ and promotes its excretion.

- Thus in **Adrenal Cortex insufficiency** decreased Aldosterone levels .
- Decreased K+ excretion and **leads to Hyperkalemia.**

Disorders Of K^{+} Metabolism

Hyperkalemia

- Hyperkalemia is increased **K^+ levels more than 5 mEq/L** .

Hyperkalemia Conditions

- Dehydration Conditions
- Violent Muscular Activity
- Intravascular Hemolysis
- Addisons Disease (Adrenal Cortex Insufficiency)
- Acidosis
- Renal Failure (Decreased Excretion)

Hypokalemia

- Hypokalemia is **decreased K^+ levels more than 3 mEq/L .**

Hypokalemia Conditions

- Starvation
- **Insulin Therapy**
- Cushing's Syndrome

(Increased Adrenal Cortex Activity)

- Alkalosis

Chloride Metabolism

- Chloride is a **Macromineral and an Electrolyte of human body.**
- Chloride is **negatively charged anion liberated from NaCl.**

The metabolism of Na+ and Cl^- goes parallel

RDA OF Chloride

- The daily requirement of Chloride is in the form of **NaCl is 5-10 gm/day.**

Dietary Sources

- Common Salt (NaCl)
- Whole grains
- Green Leafy Vegetables.
- Eggs
- Milk
- Chlorinated Water

Absorption Of Chloride

- Dietary Chloride is **almost totally absorbed from the GIT.**

Blood And CSF Chloride

- Serum Chloride Levels= 95-105 mEq/L
- CSF Chloride Levels= 125- 130 mEq/L

- **C.S.F Chloride is higher than serum Chloride**
- Since in **CSF the concentration of Proteins is very low** as compared to Serum Protein Levels.
- The higher **CSF Chloride maintains the osmotic pressure** and **Donan Membrane Equilibrium.**

Functions Of Chlorides

- **Chloride is an anion**, serves as an electrolyte of body
- It **maintains osmotic pressure** along with other Electrolyte and **regulate water balance.**

- Chloride has **role in Acid Base Balance by Chloride Shift related to RBC's.**

- **Cl- is essential for** production of **gastric HCl for digestion process.**

- Enzyme Amylase requires Chloride as cofactor.

Excretion Of Chloride

- The **excretion of Cl^- and Na^+ is parallel**.

- The **renal threshold** for **Cl^- is about 110 mEq/L**

- The **retention of Na^+ will retain Cl^-** in the body.
- **Aldosterone** has influence on **Na^+ retention which retains Cl^-**

Disorders Of Chloride Metabolism

- The Chloride and Sodium ions goes simultaneously.
- Conditions increasing Sodium also increases Chloride and vice versa.
- **Chloride and Sodium has direct relationship.**

- The Chloride(**Cl^-**) and Bicarbonate ($HCO3^-$) ions **have inverse relationship.**

- In **Acidosis** there is **decreased $HCO3^-$ and increased Cl^-**

- In **Alkalosis** there is **increased $HCO3^-$ and decreased Cl^-**

Hyperchloremia

- Hyperchloremia is increased Chlorides in serum.
- **Excess intake of salt with insufficient of water**.
- **Parenteral infusion of Saline** (I.V infusion)

- **Dehydration without loss of Salts.**
- **Cushings Syndrome**(Retention of Na^+ and Cl^-)
- **Acidosis** increases Cl^-
- **Nephritis** (Decreased excretion of Cl^- by kidneys

Hypochloremia

- **Hypochloremia is decreased Chlorides in serum**
- Less Intake of Salt
- Severe vomiting and Diarrhoea (Loss of Salt)

- **Congestive Cardiac Failure**

  (Sweating looses Salt)

- **Addisons Disease**

  (Decreased Renal Reabsorption)

- **Alkalosis** (Increases $HCO3^-$ Decreases Cl^-)

- **Kidney Dysfunction** where there is **no renal reabsorption of Cl^-**

Study Of
Trace Elements

Iron Metabolism

Iron

- Iron is an **essential trace element** of human body.
- It is an **important component of many essential vital biomolecules** vital for human body.

RDA of Dietary Iron

- Adult Man =**10 mg/day**
- Menstruating Women = **18mg/day**
- Pregnant and Lactating Women= **40 mg/day**

Dietary Type Of Iron

Two Types of Iron in Food

❖Heme Iron

- ❖ Derived from the Hemoproteins viz Hemoglobin and Myoglobin
- ❖Present in Animal Foods
- ❖Meat ,Liver tissue
- ❖Plant foods do not contain any Heme Iron .

❖Non-Heme Iron

- ❖ Derived mainly from **Plant foods**
- ❖Cereals ,Legumes, Nuts, Dates Fruits and vegetables.

- The Iron in Meat is approximately
  - 40% Heme Iron
  - 60% Non-Heme Iron

Dietary Sources Of Iron

- **Rich Sources Of Iron-**
- **Organ Meat** Like Liver ,Heart Kidney and **Jaggery**.
- **Good Sources of Iron-**
- Dates, Nuts, Green Leafy Vegetables, Pulses, Cereals, Apples and Spinach.
- **Poor Sources**
- -Milk , Wheat and Polished Rice.

IRON IN VEGETABLES

VEGETABLES	IRON IN /mg
Mushroom, pleurote	1.74
Potatoes	0.76
Cabbage, Collards	0.19
Cabbage, Green	0.59
Roasted Pumpkin and Squash Seeds	15
Spinach	2.71
Sesame Butter(Tahim) and Seeds	14.8
Sundried Tomatoes	9.1
Dried Apricot	2.2
Lentils	6.20

IRON IN FRUITS

FRUITS	IRON IN/mg
Apples, without skin	0.07
Blackberries	0.57
Dates	1.15
Pears, without skin	0.25
Pineapple	0.37
Raspberries	0.57

IRON IN GRAINS

GRAINS	SERVING	IRON IN /mg
Wheat Flour, White Cake, Enriched	1 cup	10.03
Wheat, Soft White	1 cup	9.02
Wheat, Hard White	1 cup	8.76
Sorghum	1 cup	8.45
Corn flour, Masa, Enriched White	1 cup	8.22
Corn flour, Masa, Enriched Yellow	1 cup	8.22
Millet	1 cup	6.02
Oats	1 cup	7.36
Quinoa	1 cup	2.36
Rice Bran, crude	1 cup	21.88

HEME IRON RICH FOODS

Meat	IRON IN/mg
Beef Lean Chuck	2.9mg
Turkey Meat(Dark)	2.3mg
Chicken Leg(Roasted)	1.3mg
Tuna(Bluefin)	1.3mg
Halibut	1.3mg
Pork Chops(Loin)	1mg
White Tuna	0.9mg
Shrimp(Prawns/Camarones)	1mg
Liver	30.5mg
Clams, Oysters and Mussels	28mg

Absorption Of Dietary Iron

- **Only 10% of Dietary Iron is absorbed (1-2 mg/day).**

- The site of absorption is:
- **Duodenum and Jejunum of GIT by active transport process.**

The Absorption of Iron is Regulated at GIT level

- **The absorption of Iron is proportionately increased where Iron stores are depleted.**
  - **In growing Children's**
  - **In Iron Deficiency Anemia**

HEME IRON Absorption

- ❖ Heme Iron is **well absorbed and relatively unaffected by other factors .**
- ❖ It is influenced to some extent by the body's Iron stores.
- ❖ The average absorption of **Heme Iron in meat is about 25%.**

NON-HEME IRON Absorption

- Non Heme Iron is **not so well absorbed as Heme Iron**
  - It is affected by both the Iron status of an individual
  - Components in foods eaten at the same time.

- Absorption of non-Heme Iron can vary :
- 1% in an individual with replete stores
- 20% in an individual with depleted Iron stores .

- Generally **Non-Heme Iron absorption is less than 5%.**

- **Dietary Iron** is mostly found in **Ferric form associated with food Proteins and organic acids.**

- **Gastric HCl** releases **Ferric form of Iron in the GIT lumen**.

- **Ferric form** of Iron **(Fe^{+3}) is unabsorbable form of Iron**.

- Ferric form **is transformed to Ferrous form of Iron** at GIT **in presence of Vitamin C** (Ascorbic acid).

$$Fe^{+3} \xrightarrow[\text{Glutathione-SH}]{\text{Vitamin C}} Fe^{+2}$$

Vitamin C

Glutathione-SH

- Thus **Ascorbic acid transform non absorbable Ferric form of Iron to absorbable Ferrous form**
- Vitamin C is the **most potent enhancer Iron absorption.**

Factors Affecting Iron Absorption

Iron Absorption Promoting Factor

- **Gastric acidity- HCl** facilitates in releasing the dietary bound form of Iron to free form.
- **Vitamin C, Glutathione –Cys –SH** help in reduction of Ferric to Ferrous in GIT and make it absorbable.

- **Gastroferrin a Glycoprotein** of gastric juice **facilitates the uptake of Fe^{+2} Iron from Duodenum and Jejunum**.

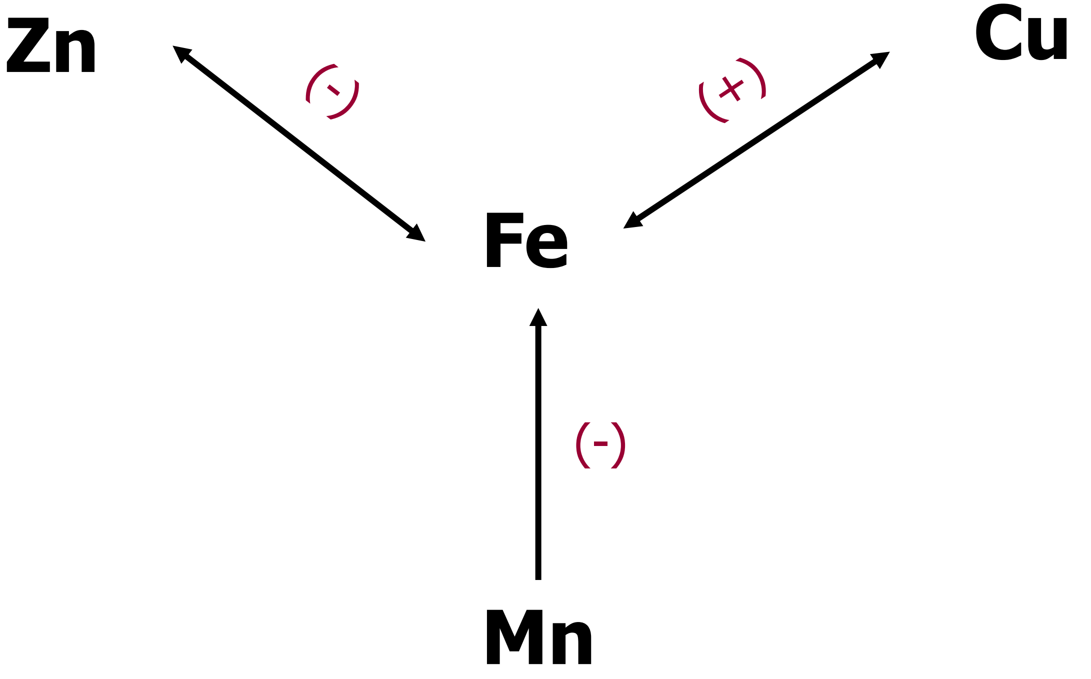
- Dietary items **promotes and facilitates Iron absorption.**
  - **Small peptides**
  - **Amino acids and**
  - **Low phosphate**

Factors Inhibiting Iron Absorption

- Alkalinity
- Phytates and Oxalates
- Long free Fatty acids (In Steatorrhoea)
- Dietary fibers

- **High concentration** of dietary **Calcium and Phosphorous inhibits Iron absorption.**
- **Low Copper** and **high lead** in body **affects Iron metabolism**.

Mineral Interactions



- **Tea and Eggs decrease Iron absorption to some extent.**

- Iron absorption is severely **impaired in patients who has undergone partial or total surgical removal of Stomach /Intestine.**

- **Absorption of Non-Heme iron (plant sources) increased by:**
  - Vitamin C
  - Meat in diet (MFP factor)
  - Citric acid and lactic acid from foods
  - HCl in the stomach
  - Sugars
- **Absorption is decreased by:**
  - Phytates and fibers (grain products)
  - Polyphenols (tea, coffee)
  - Oxalates
  - Calcium and phosphorus in milk
  - Tannic acid
  - Other minerals (calcium, zinc)

Uniqueness Of Iron

- **Iron is one way element**
- **Iron once absorbed and enter in body not excreted out through Urine.**
- **Iron is not excessively absorbed and then get excreted in urine**
- **Hence Iron is little absorbed and little/no loss.**

Regulation Of Iron Metabolism In GIT

Remembering

- Iron is not excessively absorbed from GIT
- Iron is not excreted out through Urine.

- Regulation of Iron metabolism **takes place at GIT level**
- By Intestinal Mucosal block /**Mucosal block theory of Iron absorption.**

Mucosal Block Theory
Of
Iron Absorption

- For Iron absorption at GIT level **Garnick Proposed Mucosal block theory**

- Mucosal block theory explains **the regulation of the bodies Iron content within normal state**

- **Ferrous (Fe^{+2})** form of Iron from the **intestinal lumen is absorbed**
- Made its entry into intestinal mucosal cells **through receptor mediated uptake.**

- Inside the cytosol of **Intestinal mucosal cells, Intestinal Iron Carrier (I.I.C) bind with absorbed Fe^{+2}** form of Iron.

- **Fe^{+2} form of Iron in intestinal mucosal cells** is **then oxidized to Fe^{+3} by Ferroxidase I activity .**
- This **Ferric form of Iron is temporarily stored as Ferritin form, in intestinal mucosal cells.**

- The Iron absorption from GIT lumen is regulated by:
  - The **saturation of IIC** (Carrier Iron Pool) and
  - **Adequate mucosal Ferritin content**.

- As per the bodies requirement the **temporarily stored Iron as Ferritin is released** in Ferrous form **by Ferroreductase activity.**
- The **Ferrous form of Iron from intestinal mucosal cells is then diffused in blood**.

- **Ferrous form Fe^{+2}** form of Iron diffused in blood circulation is **transformed to Ferric Fe^{+3} form in blood circulation**
- By **Ferroxidase II activity** of **Ceruloplasmin** **(A Copper containing Protein) .**

Mucosal Block Theory

- i. Duodenum and jejunum are the sites of absorption. Iron metabolism is **unique** because homeostasis is maintained by regulation at the **level of absorption and not by excretion**. No other nutrient is regulated in this manner.
- ii. When iron stores in the body are depleted, absorption is enhanced. When adequate quantity of iron is stored, absorption is decreased. This is referred to as "**mucosal block**" of regulation of absorption of iron.

Regulation of absorption

Mucosal Block Theory

- **Duodenum & Jejunum – sites of absorption**
- **Homeostasis is maintained at the level of absorption**

  Iron stores depleted absorption ↑

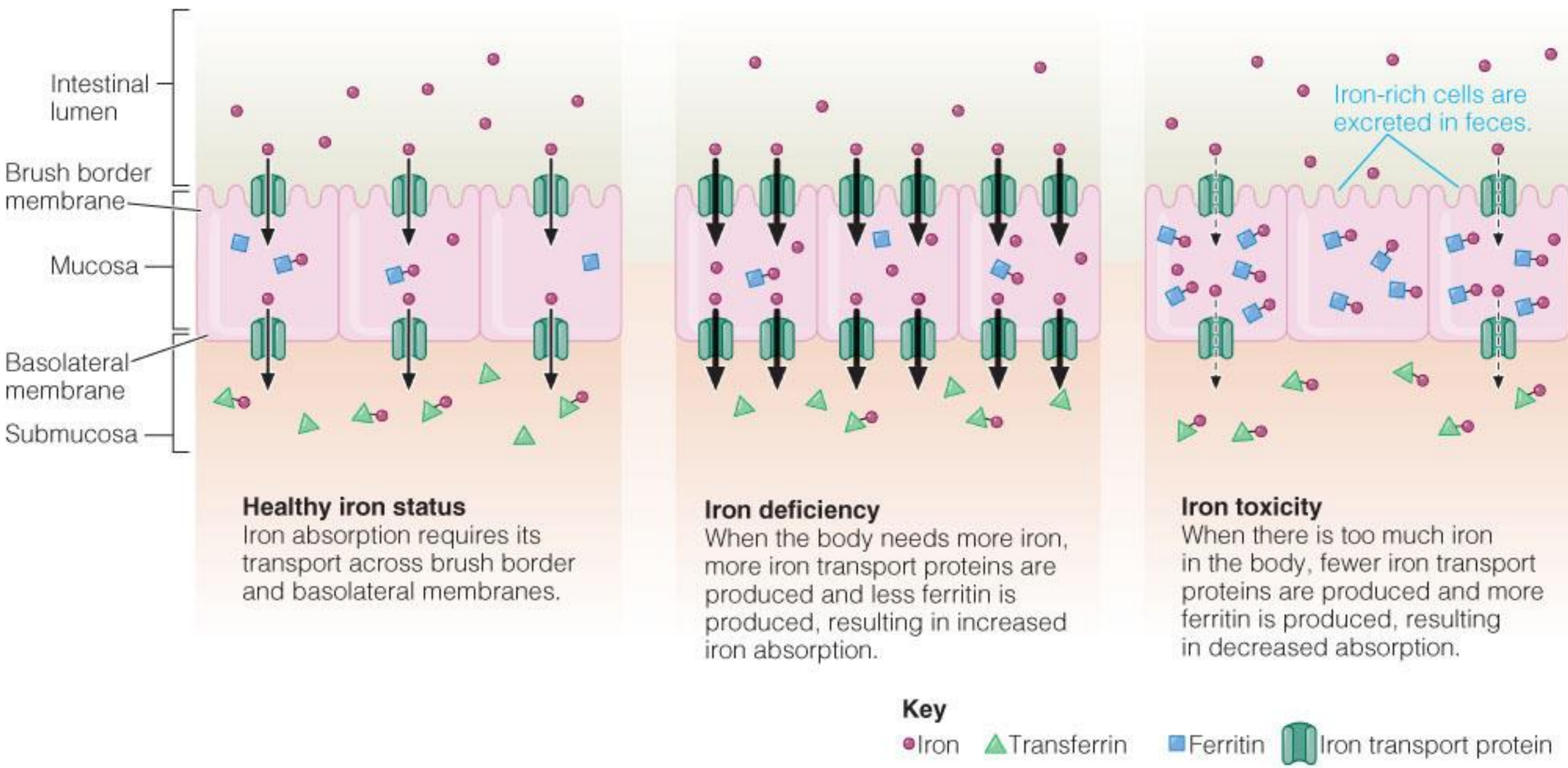
  Iron stores adequate absorption ↓
- **Only Ferrous form of Iron is absorbed.**

  Ferrous Iron binds to mucosal cell protein called divalent metal transporter-1 (DMT-1).

  This bound Iron is then transported into the mucosal cell.

  Unabsorbed Iron is excreted.

Effect of Iron Status on Iron Absorption



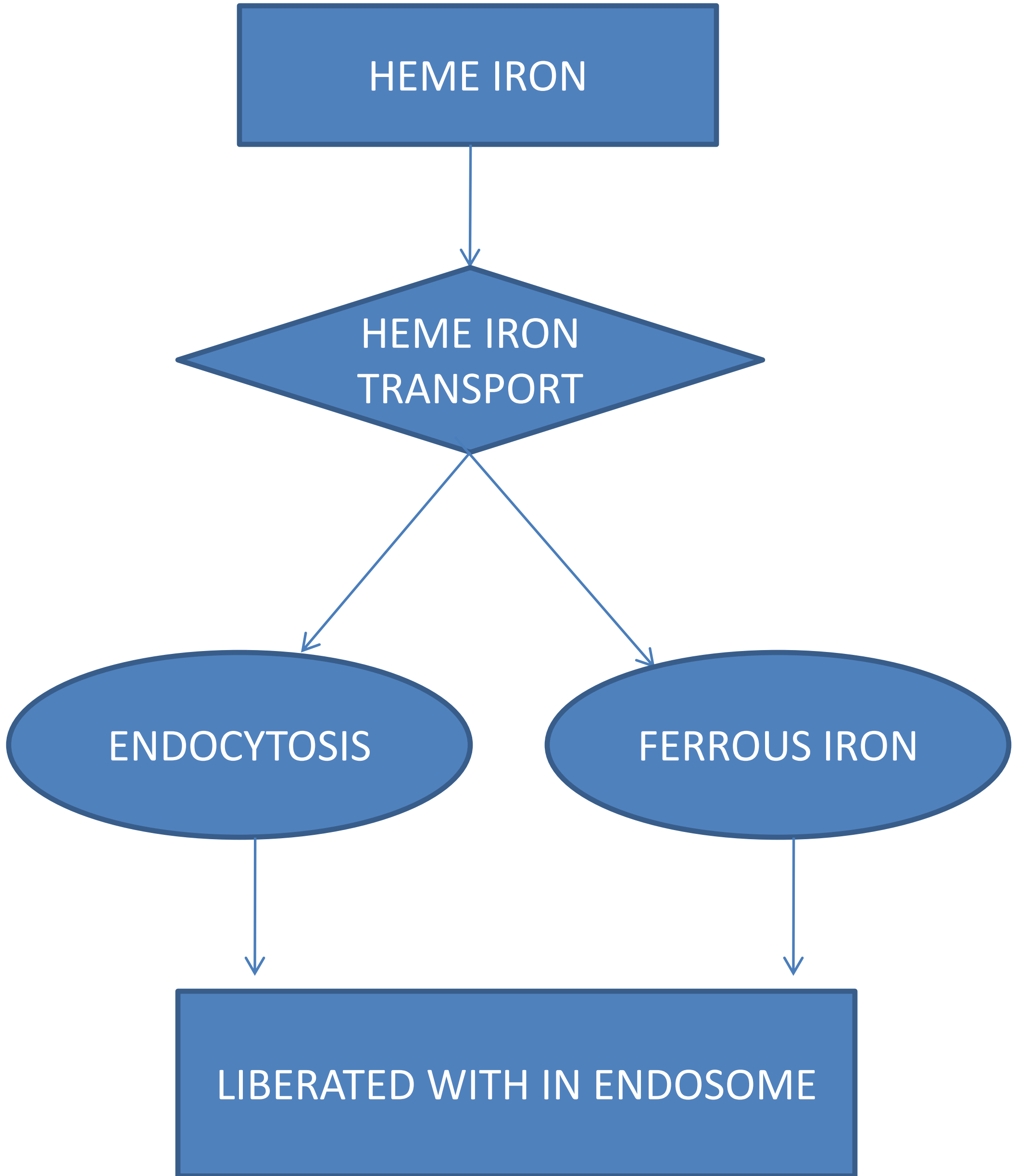
Healthy iron status
Iron absorption requires its transport across brush border and basolateral membranes.

Iron deficiency
When the body needs more iron, more iron transport proteins are produced and less ferritin is produced, resulting in increased iron absorption.

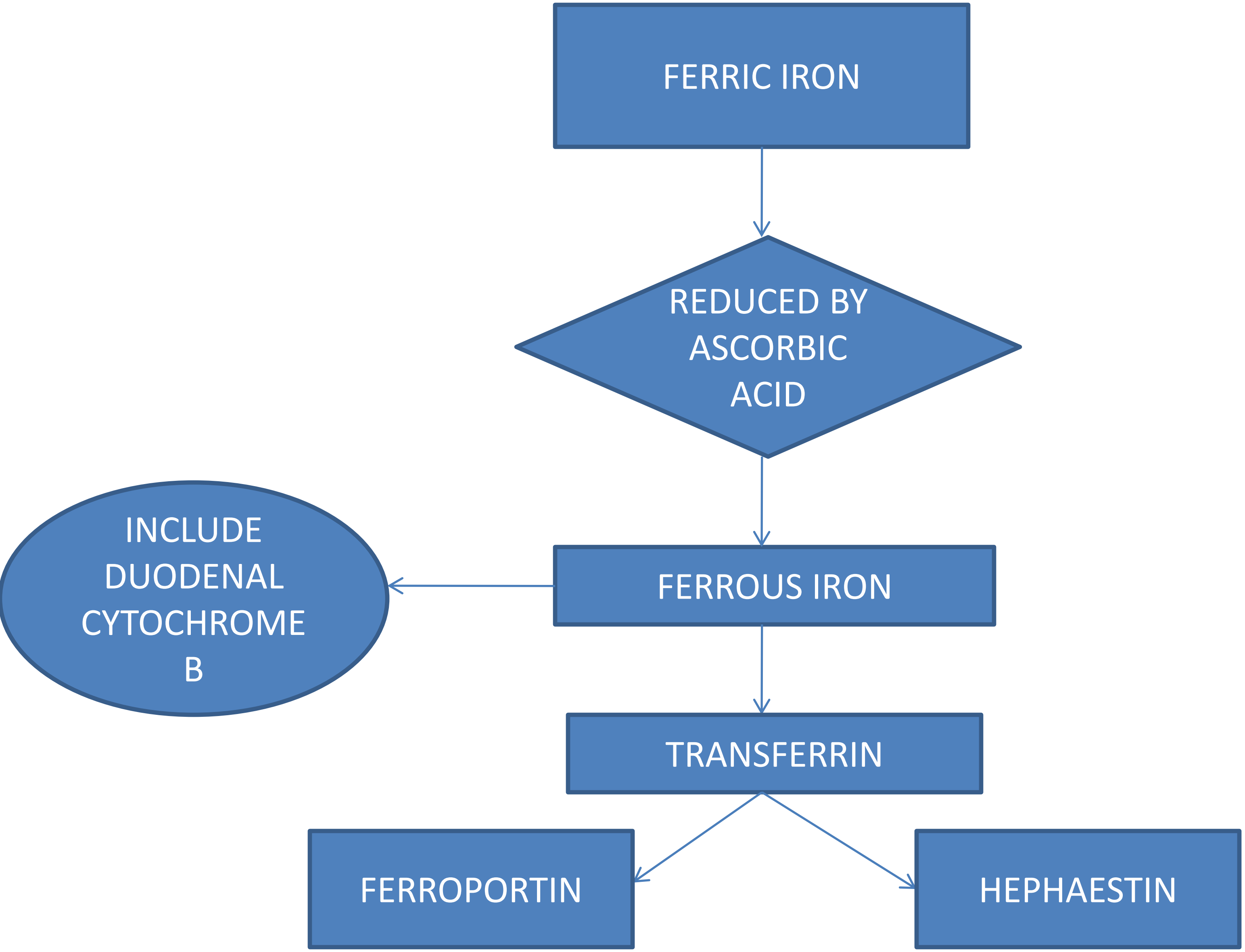
Iron toxicity
When there is too much iron in the body, fewer iron transport proteins are produced and more ferritin is produced, resulting in decreased absorption.

Key
Iron · Transferrin · Ferritin · Iron transport protein

HEME IRON UPTAKE

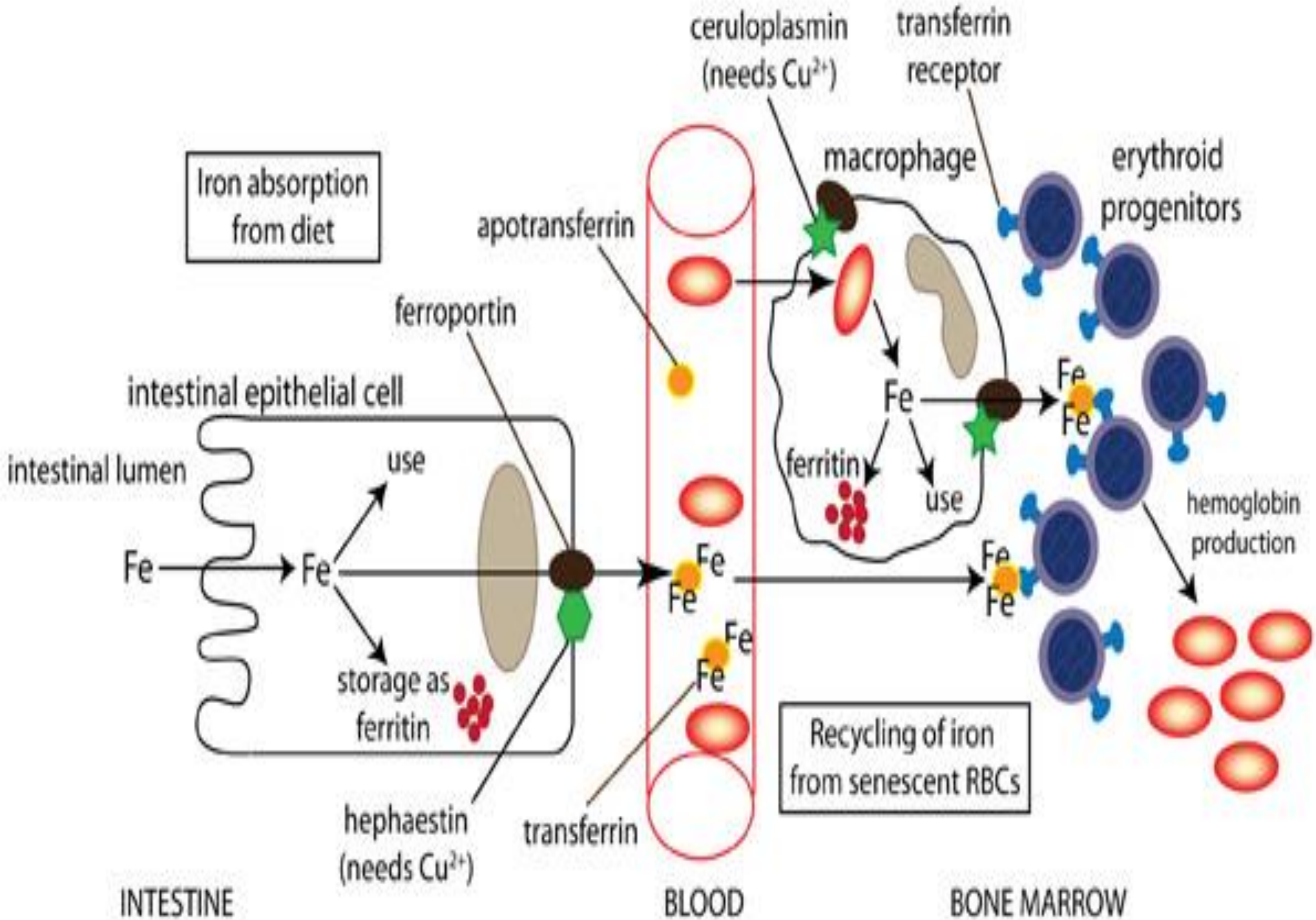


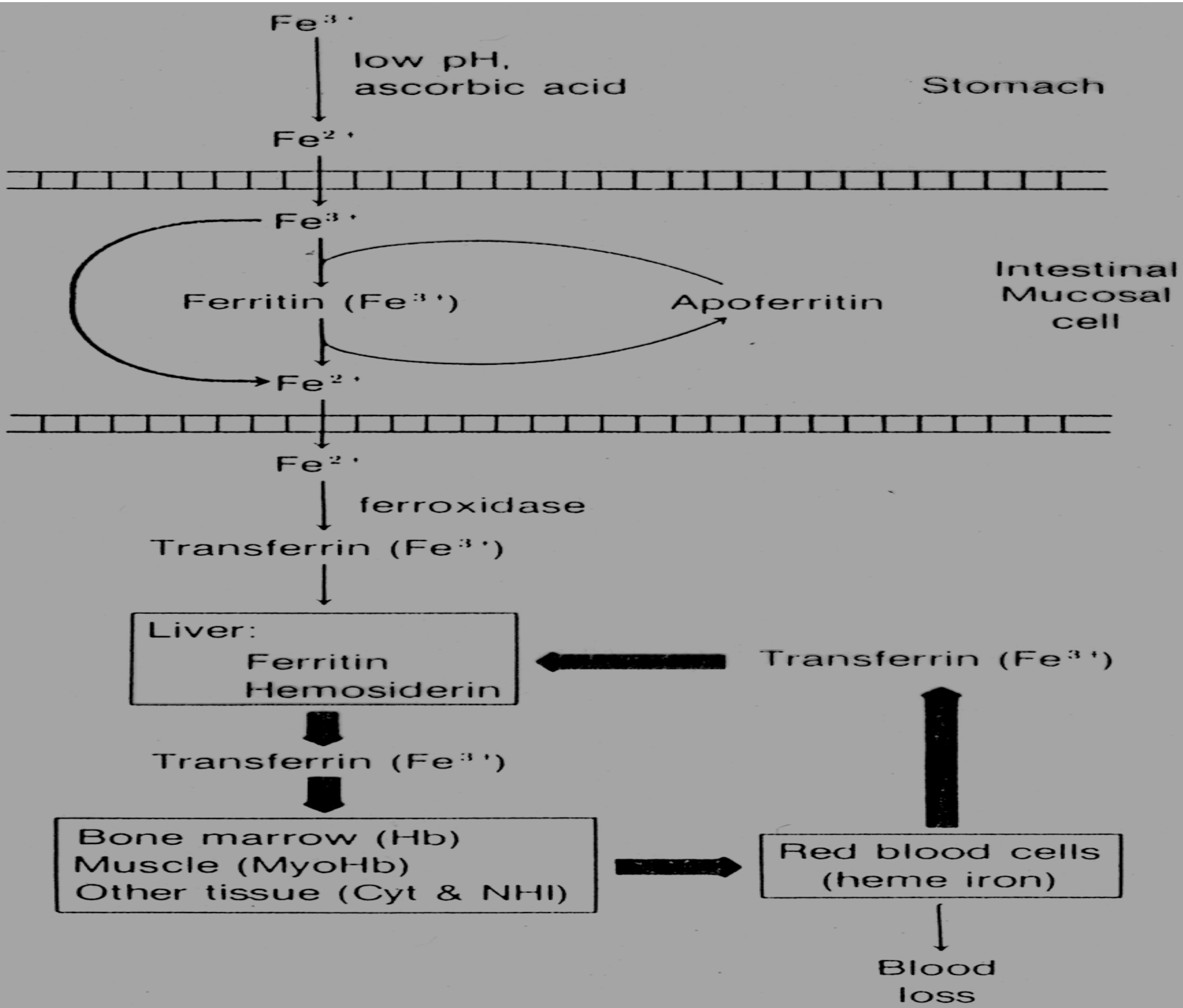
NON-HEME IRON UPTAKE



VITAMIN C IMPROVE NON-HAEM IRON ABSORPTION

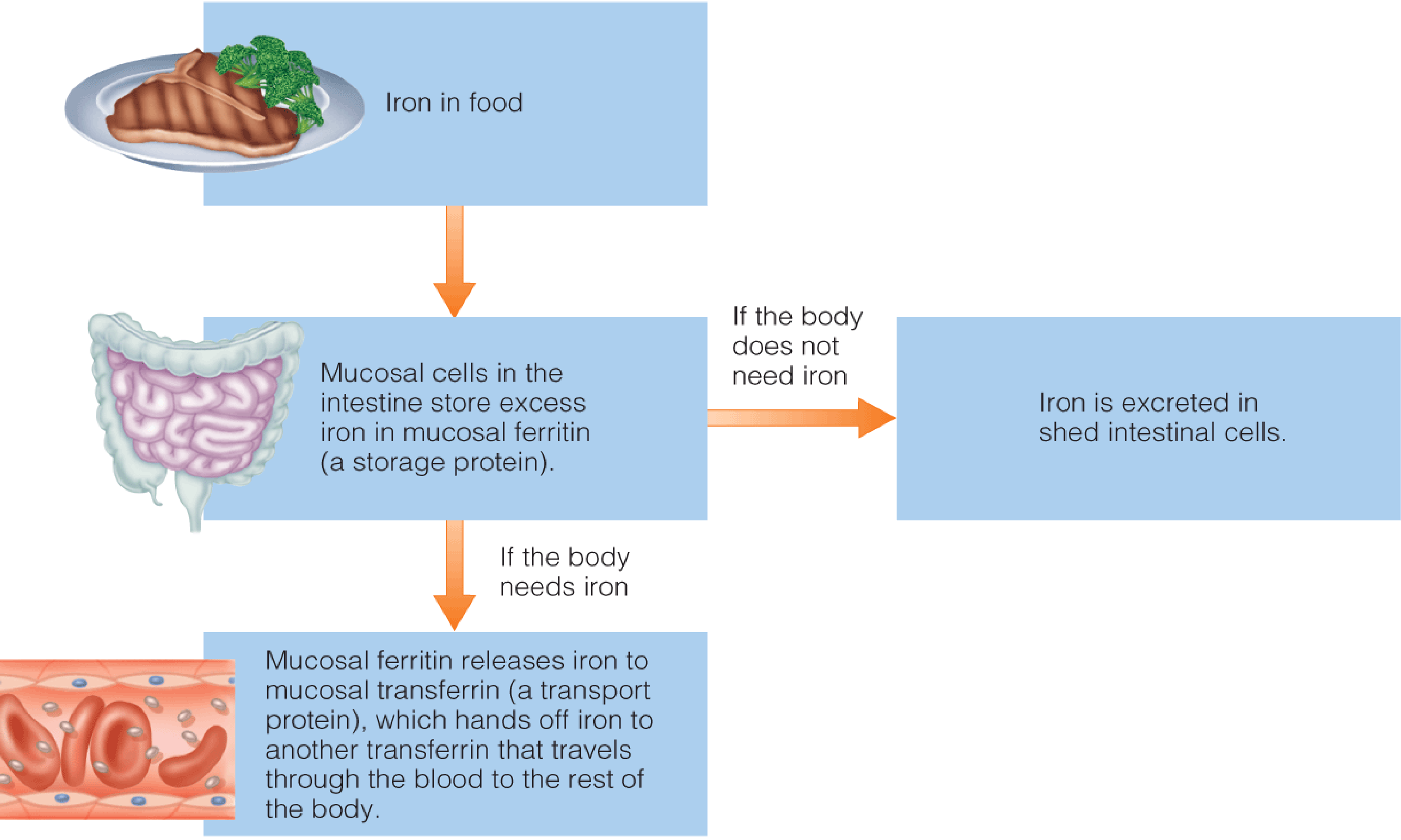
IRON ABSORPTION IN HUMAN BODY





Fe^{3+}
low pH,
ascorbic acid
Stomach
Fe^{2+}
Fe^{3+}
Ferritin (Fe^{3+})
Apoferritin
Intestinal
Mucosal
cell
Fe^{2+}
Fe^{2+}
ferroxidase
Transferrin (Fe^{3+})
Liver:
Ferritin
Hemosiderin
Transferrin (Fe^{3+})
Transferrin (Fe^{3+})
Bone marrow (Hb)
Muscle (MyoHb)
Other tissue (Cyt & NHI)
Red blood cells
(heme iron)
Blood
loss

Iron Absorption



Transport Of Iron In Blood

Transport Of Iron

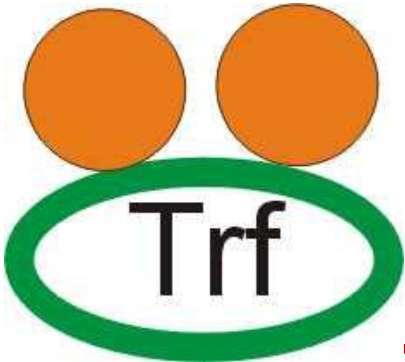
- Transport of Iron through blood is **accomplished**
- With the **help of a specific Iron Transport Protein Transferrin.**

- **Transferrin** is chemically a **Glycoprotein with mol.weight 90,000 daltons.**

  Transferrin is a **beta Globulin plasma Protein.**

Iron Transported By Transferrin

- **Apo transferrin** is a Protein, **not bound with Iron.**
- **Apo transferrin binds with two atoms of Fe^{+3} form of Iron** and get transformed to **Transferrin/Siderophillin .**



Transferrin

- **Transports Iron in the blood**
- Contains only **2 atoms of Iron in Ferric state**
- Transferrin is the **only source of Iron for Hemoglobin**
- **Transferrin saturation** is **clinically useful for Iron metabolism studies**

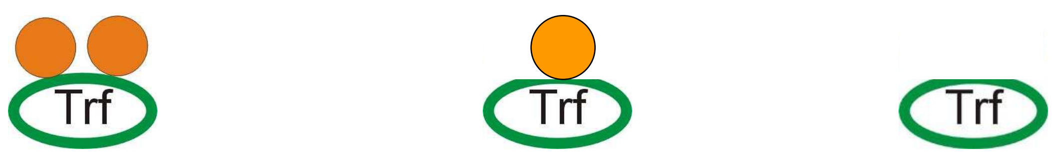
Total Iron Binding Capacity (TIBC)

- The plasma **Transferrin concentration is 250 mg%**
- **Transferrin can bind 400 µg of Iron/dl of plasma**.
- This is known as **Total Iron Binding Capacity Of Iron (TIBC).**

- **Transferrin Saturation:**

- Normal about **30-50** %

- Transferrin saturation under 15 %= Iron deficiency


Trf
Trf
Trf

- **TIBC is reduced** in patients suffering from **Iron Deficiency Anemia and Liver Diseases**.

- **High concentration of TIBC** is **noted in Iron toxicity.**

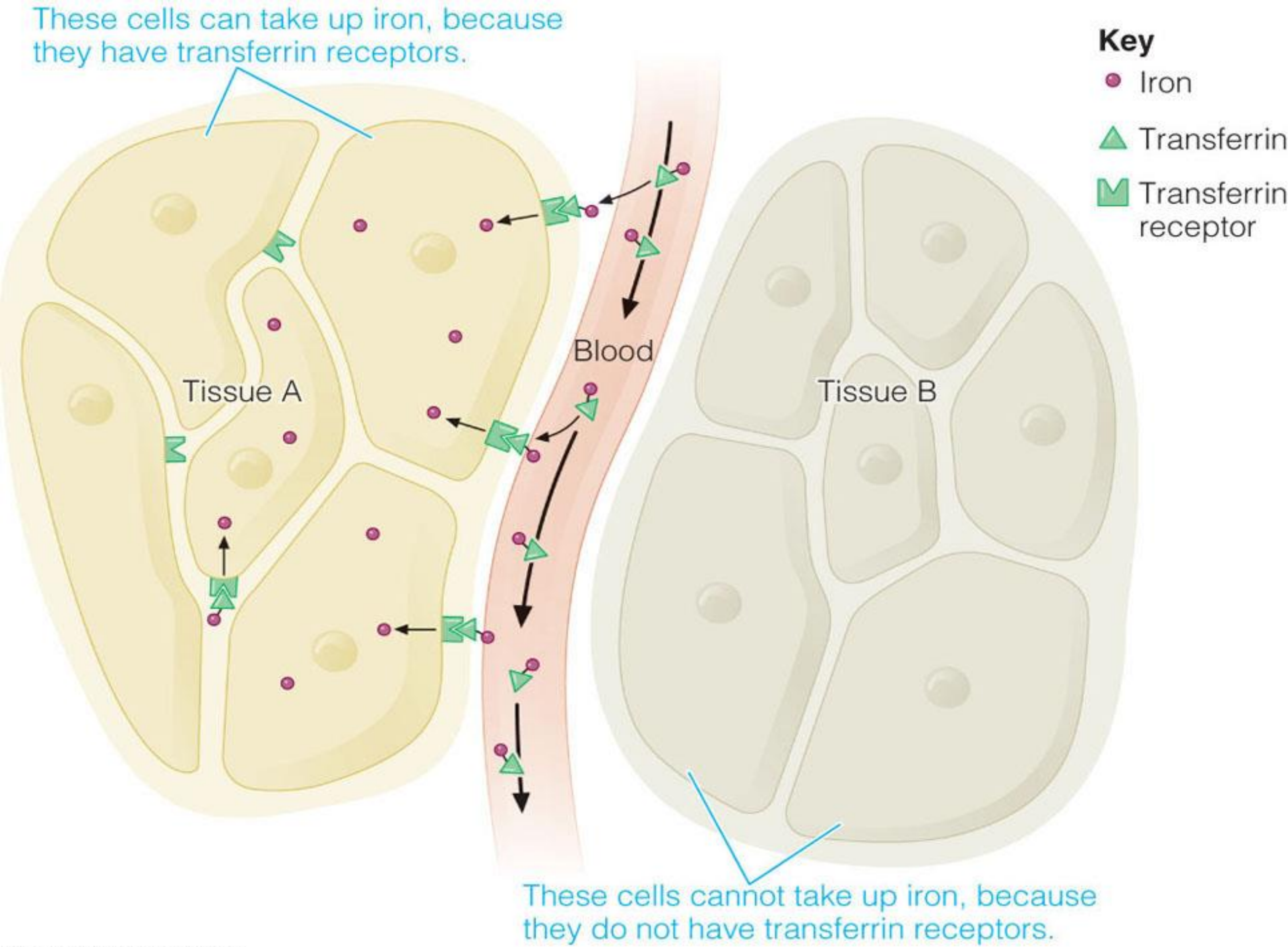
Iron Uptake By Cells

- The Cells of **various tissues have specific receptors for Transferrin**.
- **An Iron Transferrin Receptor Complex is formed and Iron is internalized within the cells**.

- **Transferrin receptors** are richly present on:
  - **Liver**
  - **Spleen**
  - **Bone Marrow**
  - **Pancreas**

Iron Circulation, Uptake Into Cells, & Storage

- **Transferrin**
  - Delivers Iron to body cells through
  - Transferrin Receptors


These cells can take up iron, because they have transferrin receptors.
Key
Iron
Transferrin
Transferrin receptor
Blood
Tissue A
Tissue B
These cells cannot take up iron, because they do not have transferrin receptors.

Storage Of Iron As Ferritin

- Iron is **normally stored in Liver, Spleen and Bone marrow**

- **Iron is temporarily** stored in the **form of Ferritin till it get utilized.**

- **Apoferritin** is a **Glycoprotein of 500,000 daltons mol.wt**

- **Apoferritin is not bound to Iron.**

- An Apoferritin can bind with **4,000 atoms of Ferric form of Iron and form Ferritin.**

- Ferritin protein **consists of 24 subunits**

- Ferritin **stores are approx. 25% of Iron on weight basis**.

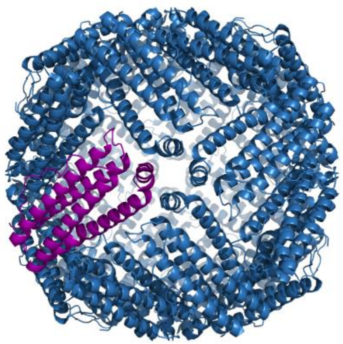
- Inside the Ferritin shell, **Iron ions form crystallites together with phosphate and hydroxide ions.**

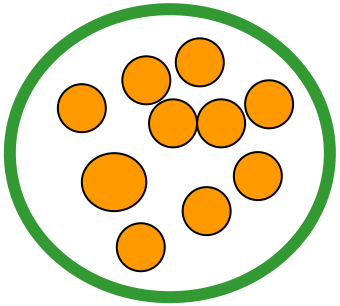
Ferritin:

Iron Storage protein

In men, Ferritin contains up to

1 gram of Iron





- **Ferritin levels reflects the amount of BODY IRON STORES**

- **Men: 20-275 µg/litre**
- **Women: 15-200 µg/litre**

- **15 µg/ litre and less: insufficient Iron stores**

Hemosiderin

- **Hemosiderin is Iron complex Proteins**
- Found in tissues in **Iron toxic conditions.**
- Hemosiderin is **Ferritin with partially stripped shell.**

- **Hemosiderin contains Ferric form** of **Iron stored around 35% on weight basis.**
- Hemosiderin is **rather insoluble form and mobilization of Iron is much slower from Hemosiderin than Ferritin.**

Body Distribution Of Iron

Body Distribution Of Iron

- **Total Iron content** of an adult body **varies and ranges from 2-5 grams.**

- About **70% of Iron is present in RBC's associated to Hemoglobin**

- **5% of Iron is present in Muscles associated to Myoglobin**.
- **Remaining 25 % in other cells associated to Heme and non Heme compounds.**

Role Of Iron In Human Body

Functions Of Iron

- Iron is an **essential trace element**
- Iron is utilized for the **biosynthesis of various Iron containing functional biomolecules.**

- **Iron is a component** of **Prosthetic group Heme** which in turn forms **various Hemoproteins:**
  - Hemoglobin
  - Myoglobin
  - Cytochromes
  - Glutathione Peroxidase
  - Catalase
  - Xanthine Oxidase
  - Tryptophan Pyrrolase

- **Iron Involved In Oxygen Transport & Storage:**
  - Hemoglobin
  - Myoglobin

- **Iron Involved In Electron Transport & Energy Metabolism(ATP)**
  - Cytochromes
  - Fe-S proteins

- **Iron In Drug Detoxification:**
  - **Cytochrome P450**

- **Substrate Oxidation & Reduction**

  – **Iron dependent Enzyme-**

  – Ribonucleotide reductase
  – Amino acid Oxidases
  – Fatty acid Desaturases
  – Nitric oxide Synthetase
  – Peroxidases

- **Iron serve as an inorganic cofactor for following Enzymes:**
  - NADH Dehydrogenase-FeS Proteins
  - Succinate Dehydrogenase-Iron Sulfur Proteins
  - Aconitase
  - Cytochrome Oxidase
  - Acyl-CoA Dehydrogenase
  - NADH Reductase

Iron Content in Hemoproteins

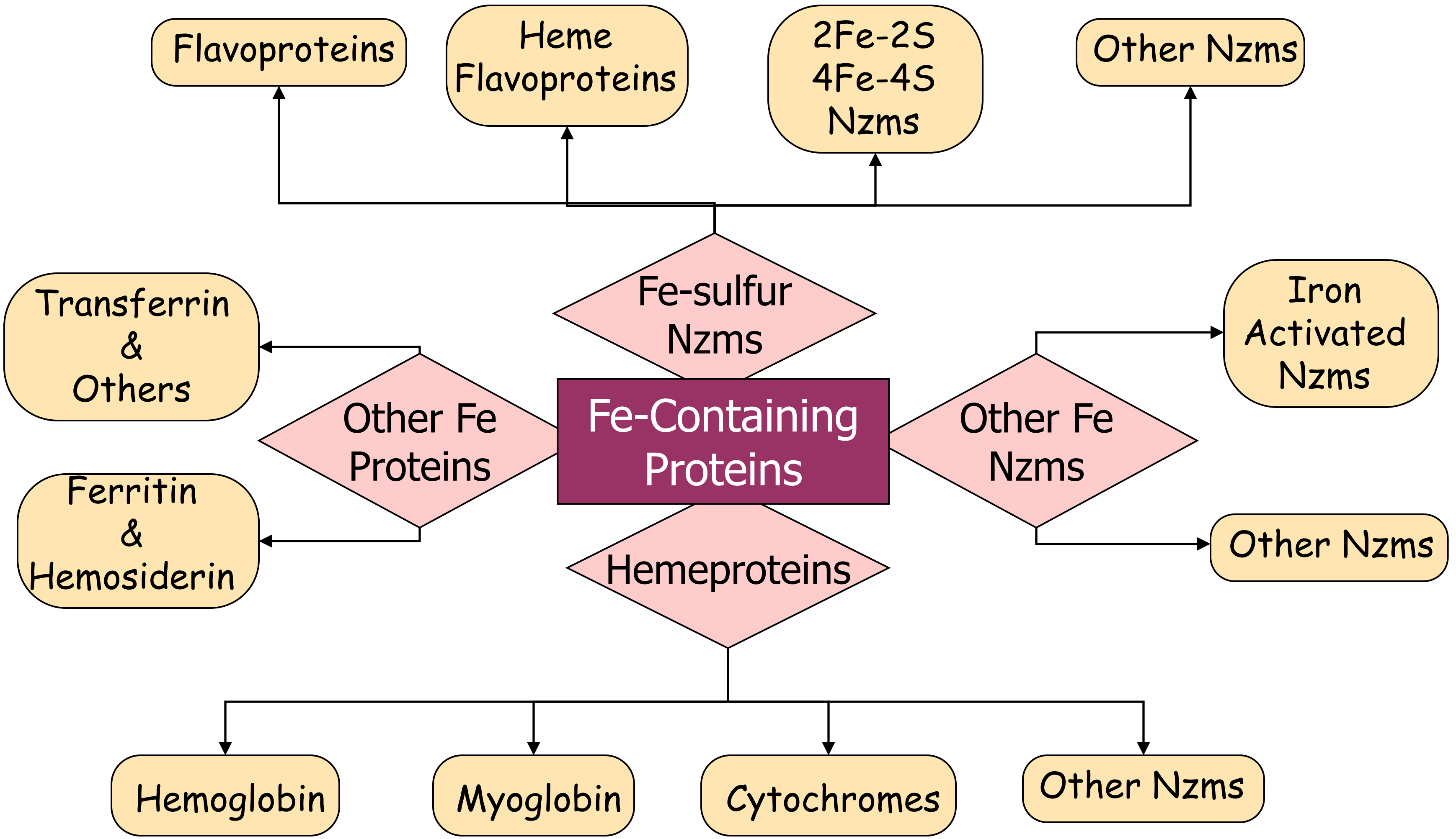
- **Hemoglobin**: more than one half of total body iron **(2.5 grams)**

- **Myoglobin**: **about 0.3 grams Fe**, muscle oxygen storage protein

- **Cytochromes** of the mitochondrial respiratory chain **(100 mg of iron)**

- **Cytochrome P450**: most abundant Hemoprotein of the liver **(about 1 mg)** detoxifies foreign compounds

Function



Flavoproteins
Heme Flavoproteins
2Fe-2S 4Fe-4S Nzms
Other Nzms
Fe-sulfur Nzms
Transferrin & Others
Other Fe Proteins
Fe-Containing Proteins
Other Fe Nzms
Iron Activated Nzms
Ferritin & Hemosiderin
Other Nzms
Hemeproteins
Hemoglobin
Myoglobin
Cytochromes
Other Nzms

Non - Heme Iron Proteins Of Body

- **Ferritin** - Iron storage protein

- **Transferrin:** Iron transport protein

Excretion Of Iron

Conservation Of Iron In Human Body

OR

Iron Is One Way Element

- Iron is a **rare element**
- It is **produced and present in deep core of Earth surface** .
- Since it contains comparatively little Iron, hence Iron is considered **as very precious element for biological system.**

- The dietary Iron has to **face many interferences in GIT** with many factors.

- **Only 1-2 % of dietary Iron succeed to get absorbed inside the intestinal mucosal cells**.

Note

- Iron absorption and release in blood stream is **regulated by Hepcidin** to maintain the body Iron stores.

- **Iron is conserved recycled** and **reutilized within the body cells.**

- **Iron is said to be one way element since**
  - The dietary absorbed Iron at GIT level(approx 10%) once entered in the body
  - Iron is stored and functionally reutilized.
  - **Almost no Iron is excreted out through urine**.

- The Hemoglobin (Hb) and Heme (Iron containing compounds)released from lysed RBC’s **get bound to**
  - **Haptoglobin (Hp)**
  - **Hemopexin respectively.**
- **Which prevent Iron excretion through Urine.**

- **Hb-Hp complex and Heme-Hemopexin complex prevents the excretion of Iron** through Urine and conserve the Iron within body.
- **Iron is restored as Ferritin and reutilized.**

- To **prevent Iron overload and toxicity in the body**.

- Only 10 % absorbed Iron at GIT is recycled, reutilized and conserved

Remember

- Iron absorption is regulated at GIT level depending upon:
- **Bodies demand and requirement of body cells**
- **Since Iron is not excreted through Urine**
- There is **no excess absorption of Iron at GIT level**

- Generally Body **Iron stores are greater in men than in women**

Routes Of Iron Loss

- Physiologically during **Menstruation** Iron is lost **(1mg/day).**
- During **Parturition** Iron loss is **1gm/pregnancy**
- Loss of Iron in **males is less than 0.5 mg/day.**

Only 1 mg of Iron is lost daily from the body
(*about 0.025% of total body iron*)

Nonspecific **pathways**
(sloughing of dead cells, iron excretion in bile)

In women, additional 30 mg of iron is lost monthly by menstruation
(*about 1% of total body iron*)

Loss of Iron is more from a Women's body than Men's body.

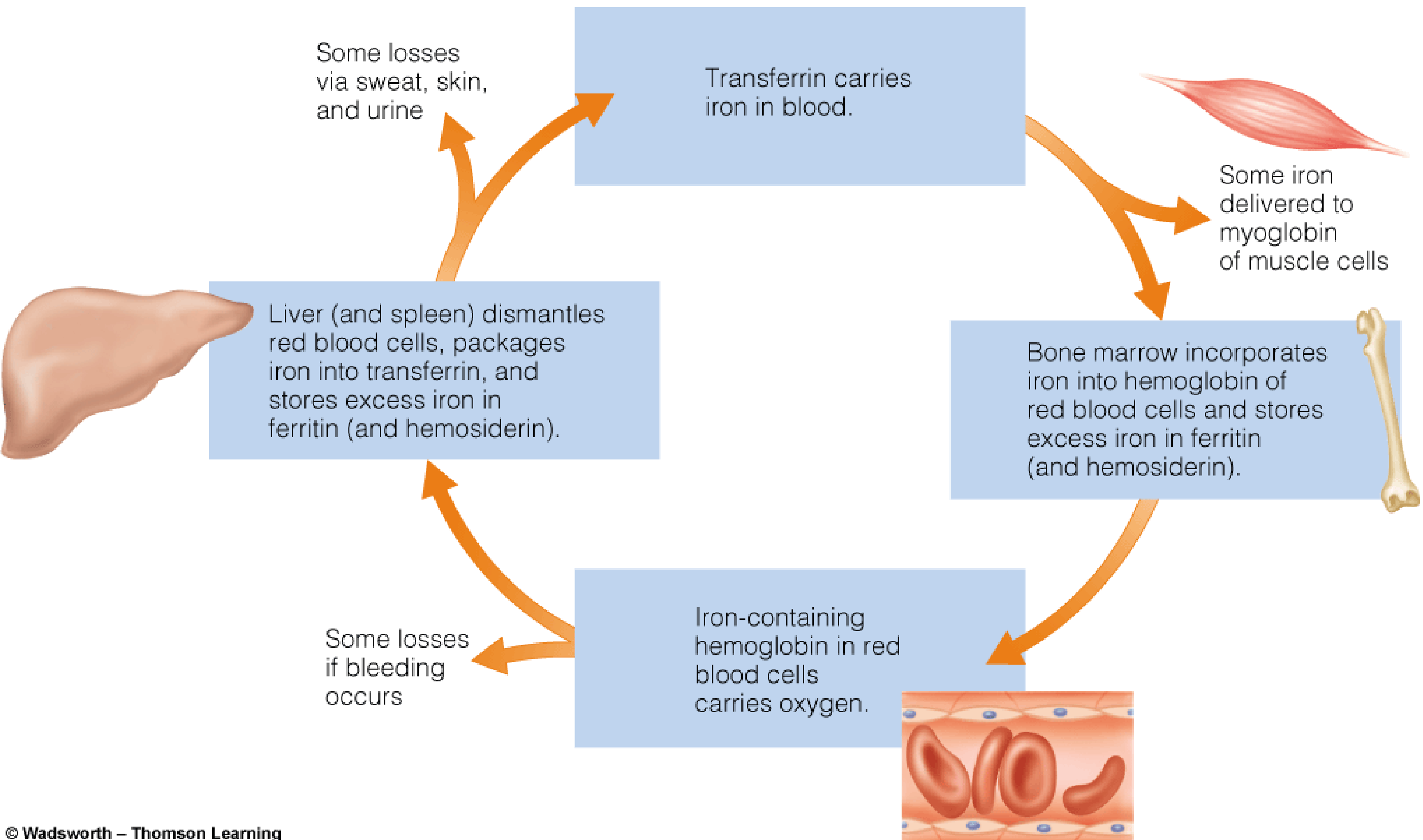
- **Feces contains unabsorbed Iron** and Iron lost due to desquamation of intestinal cells (about 30%).

- **The upper layers of skin cells contain Iron** which are being lost and becomes another source of Iron loss.

Pathological Loss Of Iron

- Excess of blood loss in cases of **Hemorrhage** due to **accidents**
- **Hemorrhoids** is another major source of Iron loss.

Iron Recycling



Disorders Of Iron Metabolism

Disorders Due To Iron Deficiency

Iron Deficiency Anemia (IDA)

- **Iron Deficiency Anemia** is **most common**
- **Nutritional deficiency disease of world population**.

Prevalence Of IDA

- **30 % of World population** is anemic due to IDA
- **70% of Indian population** is suffering from IDA.
- **85% of pregnant women** suffer from IDA.
- 15% of maternal deaths are attributed due to IDA.

Six Causes Of IDA

1. Malabsorption Syndrome:
   - Gastrectomy
   - Achlorhydria
   - Vitamin C deficiency
2. Nutritional deficiency of Iron:
   - Poverty
   - Ignorance
   - Faulty food habits

3. Chronic loss of blood

- –Hook worm Infections **(0.3 ml/day/hookworm)**
- –Bleeding Hemorrhoids (Piles)
- –Peptic Ulcers
- –Uterine Hemorrhage

4. Repeated Pregnancies (1gm/delivery)

5. Nephrosis -Kidney dysfunction leads to **loss of Haptoglobin, Hemopexin ,Transferrin** loss through Urine.

6. Copper and Ceruloplasmin deficiency: Affects Iron transport and Heme biosynthesis .

Consequences and Manifestations Of IDA

- **Iron deficiency Anemia** is characterized by:
  - **Microcytic Hypochromic Anemia**
  - **Hb less than 10 gm%**

- **Low Iron content** in human body **Lowers:**
  - **Hb levels** which in turn
    - **Decreases low Oxygen supply to tissues and cells.**
  - **Cytochrome function in ETC**
  - **ATP production**
  - **Cell activity**

Manifestations Of IDA

- Apathy **(Uninterested in Surroundings)**
- Sluggishness ,Fatigue
- Impaired attention
- Irritability
- Poor Memory
- Palpitation

Diagnosis Of IDA

- Hb Concentration
- Peripheral Smear (PS) of blood
- Serum Iron Levels
- TIBC Levels

Other Parameters: Measuring Iron Status

- Serum Ferritin
- Hematocrit
- Ceruloplasmin levels
- Vitamin C

Treatment Of IDA

- Dietary Sources Containing Rich Concentration Of Iron
- Vitamin C Supplementation
- Oral Iron Supplementation

Iron Toxicity Disorders

Hemosiderosis Iron Toxic Condition

Hemosiderosis

- Hemosiderosis is **Iron overload condition**
- Where there is **increased Iron Stores as Hemosiderin**
- In **Liver, Spleen, Bone marrow** etc **without associated tissue injury and cellular dysfunction.**

- Hemosiderosis **is an initial Stage of Iron overload**.

- **Hemosiderin** are **golden brown granules**

Causes of Hemosiderosis

- Prolonged Parenteral Iron supplements
- Repeated Blood Transfusions

- **Hemosiderosis** occurs during **treatment of Hemophilia and Beta Thalassemia**
- **Since these patients receive repeated blood transfusions.**
- **GIT level of regulation is bypassed in the parenteral infusion of blood.**

Types Of Hemosiderosis

Primary Hemosiderosis

- **Genetic cause** due to presence of **abnormal gene** on **short arm of 6th Chromosome.**
- In these cases **Iron absorption is increased at GIT level** and
- **Transferrin levels in serum are elevated**.

Acquired Hemosiderosis/ Nutritional Siderosis / Bantus Siderosis

- **Bantus are tribal** people of **Africa**.
- Who **cooked their food in Iron pots**.
- **Staple food** of them contained **low Phosphate and High Iron content.**

- **The Iron absorption is high** in the Bantus
- Gradually leading to Hemosiderosis termed as **Nutritional/Bantus Siderosis**

Hemochromatosis

What Is Hemochromatosis?

- **Hemochromatosis** is **much more severe condition of Iron overload.**

- Deposition of **large concentrations of Hemosiderin**
- In functional stores of organs **causing dysfunction and injury to these organs.**

- In Hemochromatosis **Hemosiderin is spilled out of tissues and found in blood circulation.**

- Thus there is **Hemosiderin, also deposited under skin**.

Consequences And Clinical Manifestations Of Hemochromatosis

Iron Poisoning

- **Acute or over dosage of Iron** may lead to Iron poisoning this manifests with:
- Vomiting
- Nausea
- Diarrhea
- Hematemesis (Blood Vomits)
- Liver Damage
- Organ Dysfunctions
- Coma

- Liver Cirrhosis
- Pancreatic Damage-**Diabetes mellitus**
- Skin Pigmentation-**Bronze Diabetes**
- Hypothyroidism
- Arthritis
- Arrhythmia
- Heart failure

- **Severe Hemochromatosis** leading to **organ dysfunctions lead to death.**

- **90% of affected individuals are Males.**

Organ systems susceptible to Iron overload

Clinical sequelae of Iron overload

Pituitary	→ Impaired growth, infertility
Thyroid	→ Hypothyroidism
Heart	→ Cardiomyopathy, cardiac
Liver	→ Hepatic cirrhosis
Pancreas	→ Diabetes mellitus
Gonads	→ Hypogonadism

- **Liver is the principal site for iron storage** and has the **largest capacity for excess Iron storage**.

- When the **Liver capacity is exceeded, Iron is deposited in other organs.**

- **In patients with β-Thalassemia, Iron loading of the anterior pituitary**

- Is primarily **responsible for disrupted sexual maturation.**

- **Hemochromatosis** also leads to **Growth failure due to :**
  - **Growth hormone deficiency**
  - Defective synthesis of **Insulin-like growth factor**

Hepcidin And Its Role

Discovery of HEPCIDIN (2000)

Hepcidin: “Iron Regulatory Hormone"

What Is Hepcidin?

- **Hepcidin** is **a natural protein hormone of human body**

- **Encoded** by the **HAMP gene**.

- Hepcidin is **25 amino-acid peptide hormone.**

- Hepcidin is **synthesized by Hepatocytes.**

- It is **then transported in the blood stream for its function**.

- Hepcidin **regulates Iron absorption in blood.**

Hepcidin blocks Iron Export from:

MACROPHAGES

And

ENTEROCYTES IN THE SMALL INTESTINE

- Hepcidin is the **principal regulator of systemic/blood Iron homeostasis**

- Hepcidin **blocks Iron export from Macrophages and Enterocytes into blood circulation.**

- **Hepcidin Reduces**

- **Dietary Iron absorption** by reducing Iron transport across the gut mucosa (enterocytes)
- **Iron exit from Macrophages** the main site of Iron storage
- **Iron exit from the Liver**

Specific Action Of Hepcidin

- **Hepcidin inhibits** iron transport by binding to the **Iron export channel Ferroportin**
- Which is located on the basolateral surface of
  - Gut **Enterocytes**
  - Plasma membrane of Reticuloendothelial cells **Macrophages**

- Hepcidin controls Blood Iron concentration
- Tissue distribution of Iron by:
  - Inhibiting intestinal Iron absorption
  - Iron recycling by macrophages
  - Iron mobilization from hepatic stores.

HEPCIDIN In Inflammation

- In states of **inflammation** the **Hepcidin** level is **abnormally high.**
- In inflammation **serum Iron falls down**
- Due to **Iron trapping within Macrophages** and **Liver cells**
- **Decreased Gut iron absorption**.

- Hepcidin elevated during infections and inflammation,
- Causing a **decrease in serum Iron levels**
- Contribute to the **development of anemia of inflammation**
- Probably as a **host defense mechanism to limit the availability of Iron to invading microorganisms**.

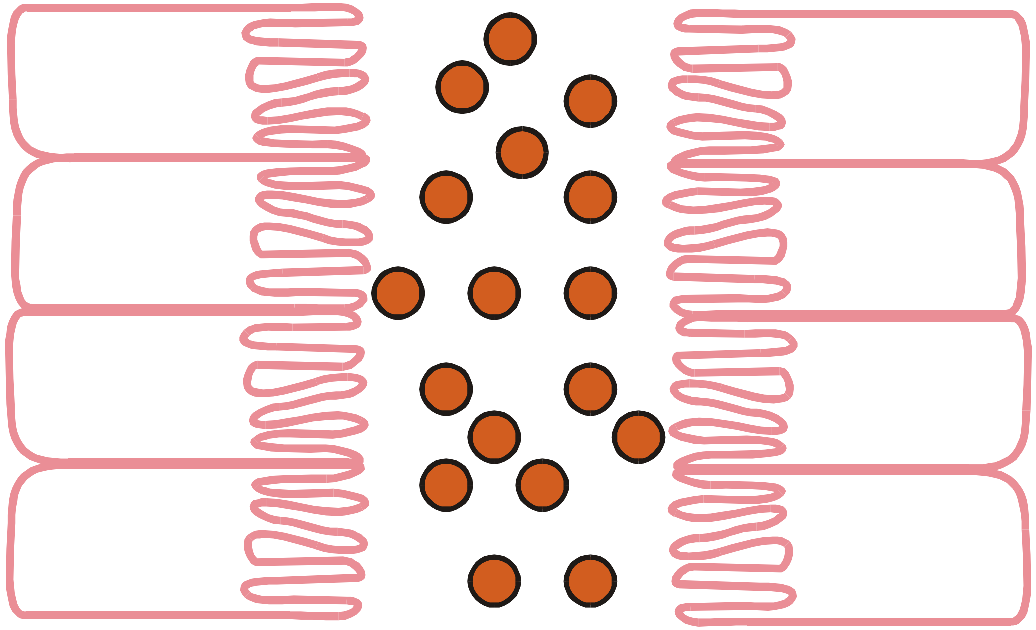
Regulation Of Hepcidin Synthesis

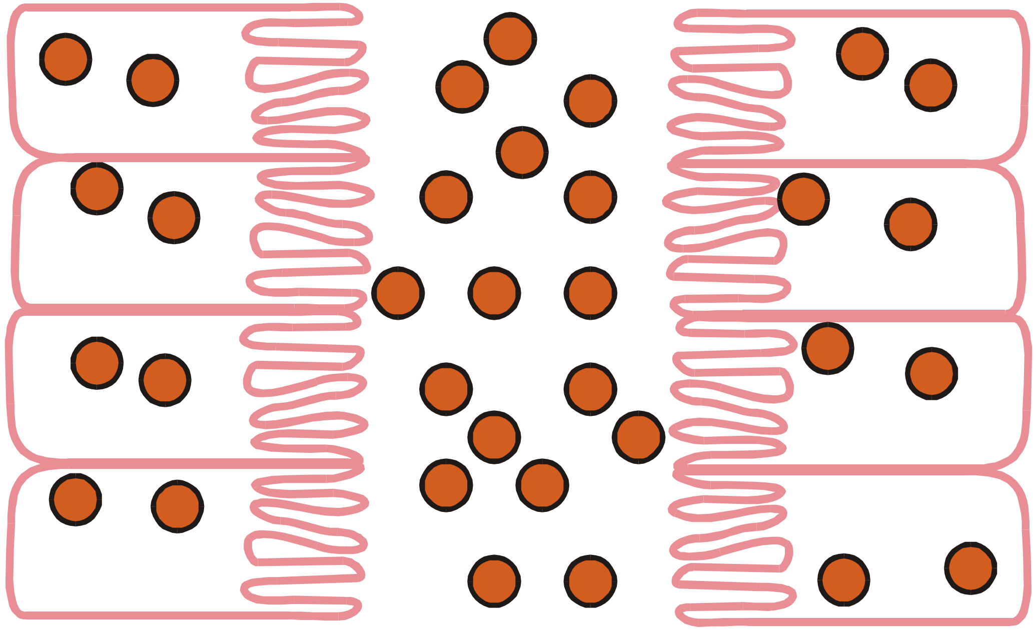
Hepcidin is released from the Liver according to body Iron status:

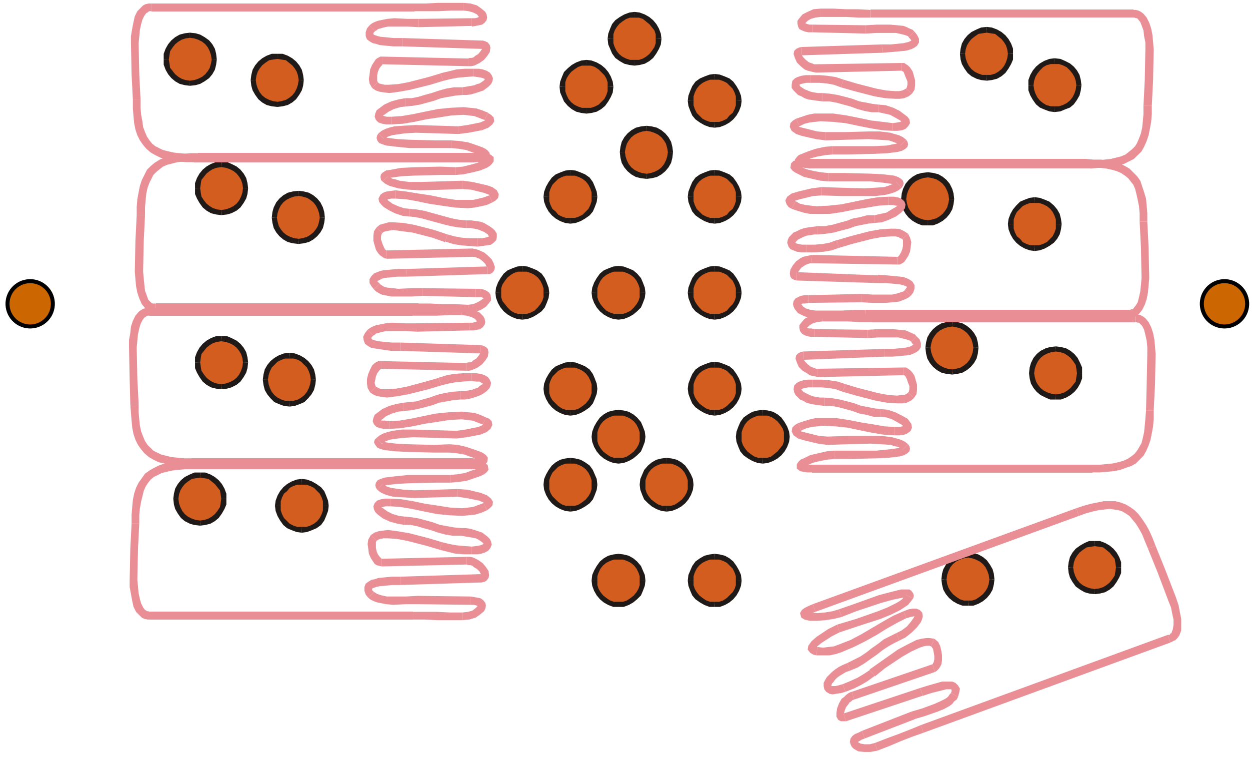
- **Iron overload increases Hepcidin expression**

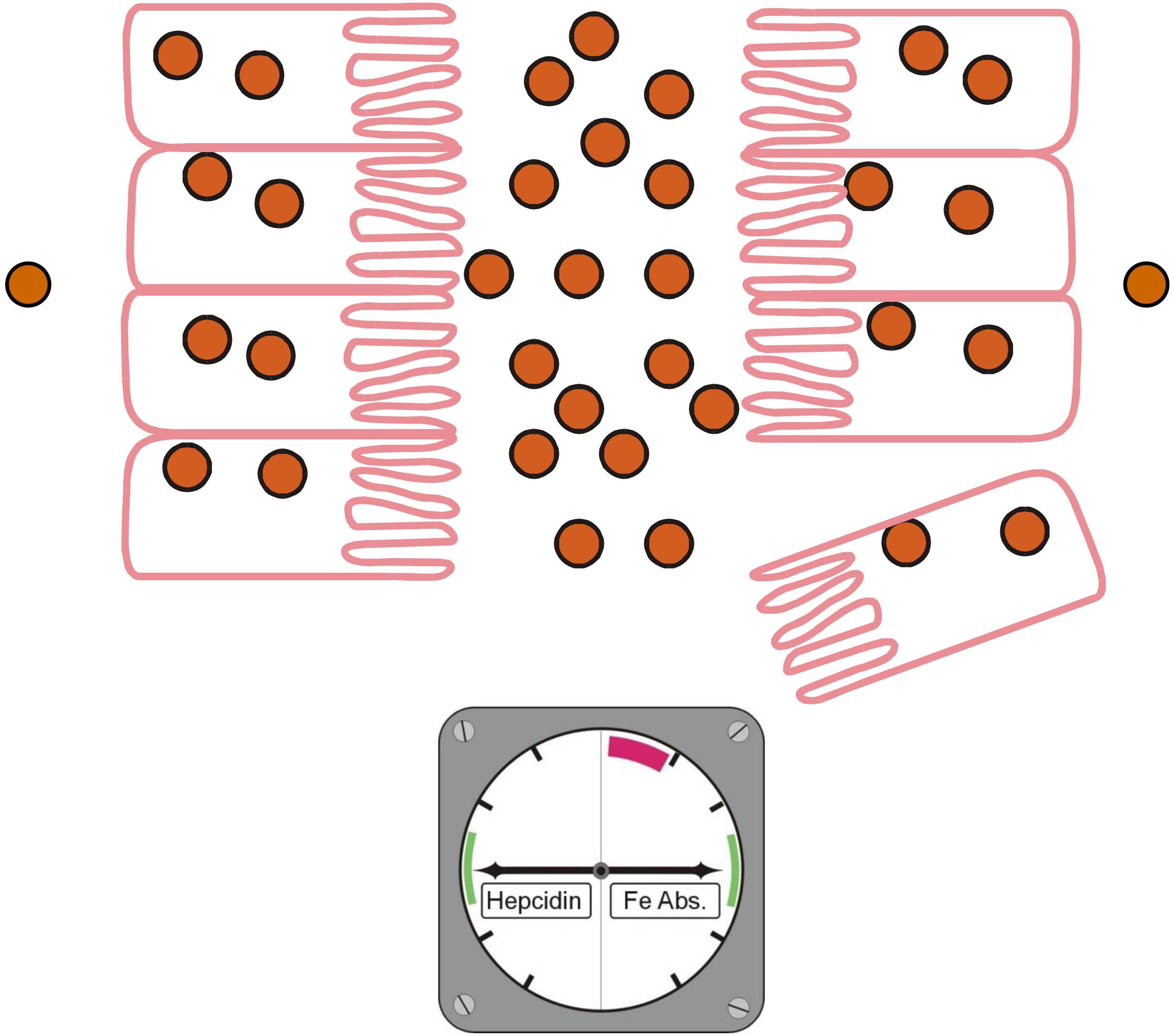
- **Iron deficiency decreases Hepcidin expression**

- **Due to mutations in the Hepcidin gene i**tself or due to mutations in the regulators of Hepcidin synthesis.
- **Hepcidin defects appears to be the ultimate cause of most forms of Hemochromatosis**.

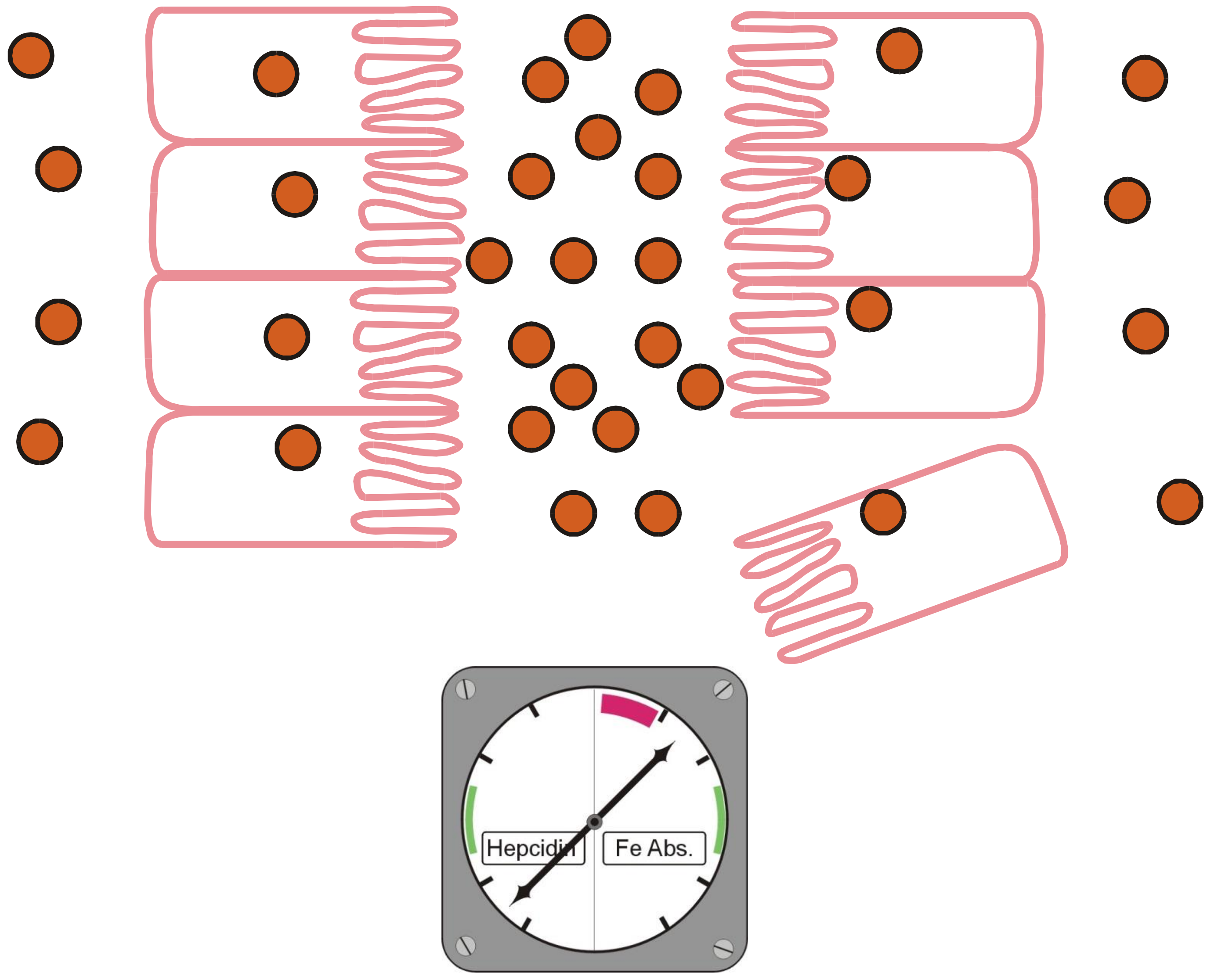


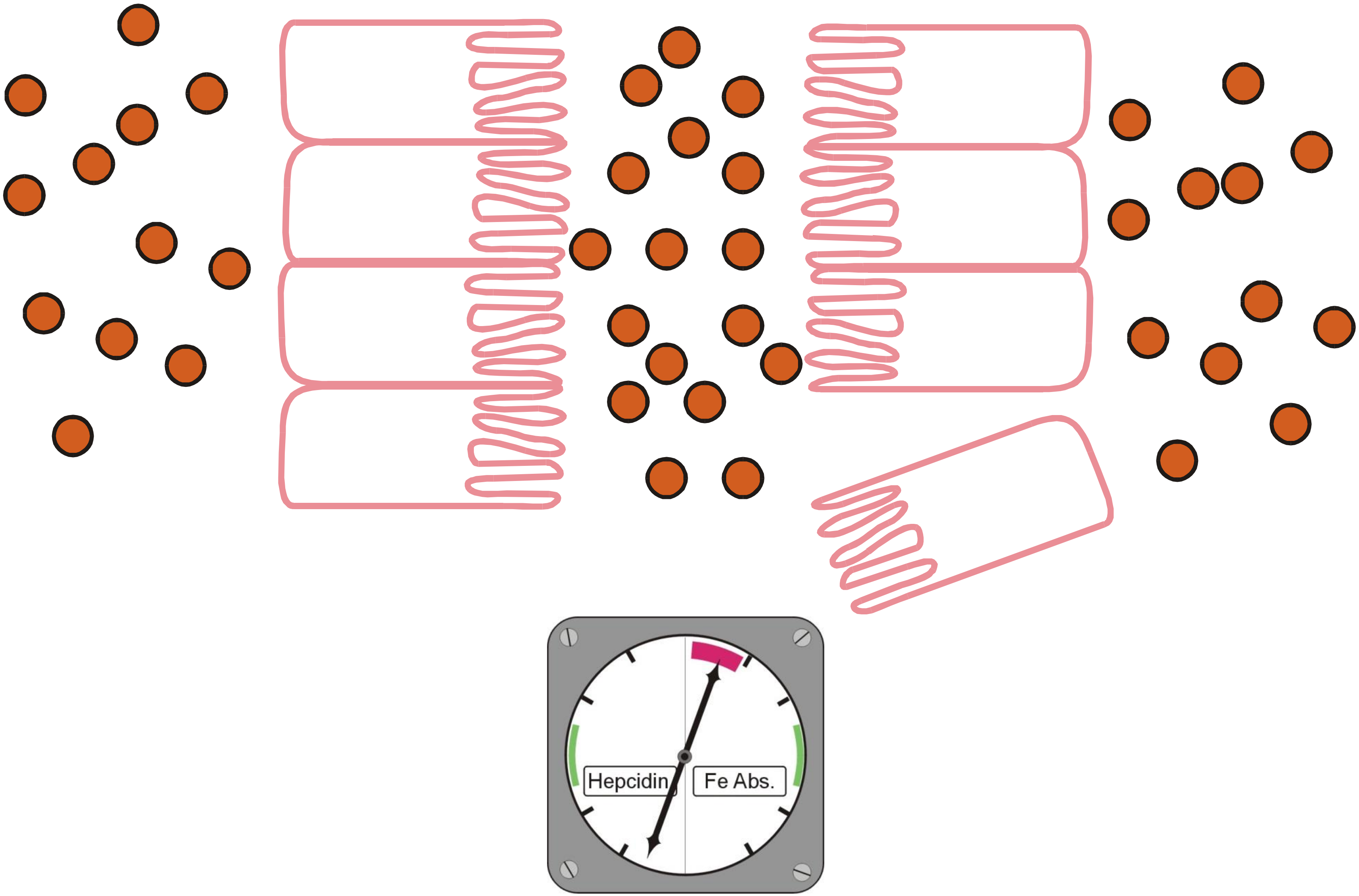






Hepcidin
Fe Abs.


Hepcidin
Fe Abs.


Hepcidin
Fe Abs.

Iodine Metabolism

Iodine

- Iodine is an **essential trace element**
- Iodine is **very vital for normal health , growth and reproduction of human body**.

RDA For Iodine

- For Adults – **100- 150 µg/day**

- **Pregnant Women-200 µg/day**

Dietary Sources

- **Iodized Salt**
- **Sea Foods**
- Fruits Vegetables grown on **sea beds**
- Onions
- Drinking Water

Absorption Of Iodine

- Absorption of Iodine is mainly **from small intestine.**
- **Small amounts** of Iodine are **absorbed through Skin and Lungs.**

Body Distribution Of Iodine

- Total body content of Iodine= **25-30 mg.**
- **80 % of Iodine is taken up by Thyroid gland.**
- Skin and Skeleton contains small amount of Iodine.
- **Blood levels of Iodine- 5-10µg%**

Functions Of Iodine

- **Iodine** is **mainly taken up by Thyroid gland.**

- Iodine is **utilized for the biosynthesis of Thyroid Hormones .**

- The **Iodine is activated** and added to **Tyrosine residues of Thyroglobulin Protein**

- To form **MIT and DIT which in turn forms T3 and T4**.

- **Iodine metabolism requires Selenium.**

- **T4 is transformed to T3** in presence of **Se containing Enzyme Delodinase.**

Functions Of Thyroid Hormones

- Thyroid Hormones **Regulate Basal Metabolism**

- **Thus Iodine regulate Carbohydrates, Lipids and Protein Metabolism**

- Iodine **develops Brain**
- **Regulate Body Temperature**

Excretion Of Iodine

- Nearly **70-80% of Iodine is excreted through Urine.**
- Small amount of **Iodine may get excreted through Bile ,Skin and Saliva.**
- **Milk of lactating women contains some Iodine.**

Disorders Of Iodine Deficiency

- **Iodine is generally scarce in soil** of Mountanious regions.
- **Upper regions of mountains contain** less Iodine such areas are called as **Goiterous belt**.

- **Deficiency of Iodine** to an **adult** human body **causes Goiter.**

- **Deficiency of Iodine** in **Children leads to Cretinism**,

- Severe **Iodine deficiency in pregnant mothers leads to**
  - **Intrauterine hypothyroidism resulting in Cretinism.**
- The condition is characterized by **mental retardation ,slow body development-Dwarfism**, **Characteristic facial Structure.**

Endemic Goitre

- **Severe Iodine deficiency** in adults leads to Endemic Goitre.
- Goitre is a condition of **enlarged Thyroid gland**
- With **decreased Thyroid hormone production** due to Iodine deficiency.

- **In Goitre enlargement of Thyroid gland**
- Due to proliferation of Thyroid epithelial cells.
- **Enlarged Thyroid gland** in Iodine deficient state is **significant**
- **To extract Iodine from blood more efficiently**.

Types of Goitre

- Simple Goitre
- Toxic Goitre

- **A simple goiter** can occur **without a known reason.**
- In this person thyroid gland is **not able to make enough thyroid hormone to meet the body's needs.**
- This can be due to a **lack of iodine in a person's diet.**
- **To make up for the shortage of thyroid hormone, the thyroid gland grows larger.**

- Simple goiters may occur in people
- **Who live** in **areas where the soil and water do not have enough Iodine.**

- **Toxic Nodular Goiter** is an enlarged thyroid gland that has a small, **rounded growth or many growths called nodules**.
- **One or more of these nodules produce too much thyroid hormone.**

Goitrogens

- These are **compounds present in food stuffs**
- Which **prevent utilization of Iodine**
- **Goitrogens leads to Iodine deficient disorder Goiter.**

- **Cabbage and Tapioca** contain **Thiocyanate**
- This **inhibits uptake of Iodine by Thyroid gland**.

- **Mustard seed** contain **Thiourea**

- Which **inhibit Iodination of Thyroglobulin during T3 and T4 hormone synthesis.**

Copper Metabolism

Copper

- Copper is an **essential trace element**
- Required for varied functions of human body **keeping it vital and active**.

RDA Of Copper

- Adults **2-3 mg/day**
- Infants and **Childrens- 0.5-2 mg/day**

Dietary Sources Of Copper

- Organ Meat
- Liver
- Kidney
- Eggs
- Cereals
- Nuts
- Green Leafy Vegetables.

Absorption Of Copper

- **About 10%** of dietary Copper is absorbed mainly by **Duodenum**.

- **Metallothionein facilitates Copper absorption by mucosal cells.**

- Phytate ,Zinc, Molybdenum (Mo^{+2}) decreases Copper uptake into intestinal mucosal cells.

Body Distribution Of Copper

- Total body content of Copper is **100 mg distributed in different organs.**

- The Copper concentration of **Plasma=100-200µg%.**

- **95% of Copper in blood** is tightly bound to a Copper containing Protein **Ceruloplasmin.**
- 1 molecule of Ceruloplasmin contains **8 atoms of Copper.**

Functional Role Of Copper

Enzymes and Proteins Containing Cu

- Copper is an essential **constituent of several Enzyme and Proteins**.

Cu- Containing Enzymes

- Cytochrome Oxidase (In E.T.C)
- Catalase (H2O2 Detoxification)

- Tyrosinase (Melanin Biosynthesis)
- **Super oxide Dismutase (SOD) an Antioxidant.**
- **ALA Synthase (Heme Biosynthesis)**
- Ascorbic acid Oxidase
- Monoamine Oxidase
- Phenol Oxidase
- **Lysyl Oxidase(Collagen Synthesis)**

- Since **Cu containing Lysyl Oxidase Enzyme is involved cross linking of Collagen Fibers of bone**
- Copper has **indirect role bone development.**

Copper Containing Proteins

- **Ceruloplasmin** (Ferroxidase II Activity)
- **Storage form of Copper**

(Liver RBCs and Brain Cells)

- **Hepatocuperin**
- **Hemocuperin**
- **Cerebrocuperin**

Role Of Copper In Iron Metabolism

Ceruloplasmin

- Ceruloplasmin is a **Copper containing Glycoprotein.**
- Ceruloplasmin is **blue colored.**
- Ceruloplasmin **contains both Cuprous and Cupric forms of Copper in its structure.**

Remember

- **Ceruloplasmin** is **not Copper transport Protein.**

- Normal Concentration of **Ceruloplasmin -25-50mg%.**

- 5% of Copper in blood is **loosely bound to Protein Albumin.**

- **Function of Ceruloplasmin in blood** is **Ferroxidase II activity.**

- **Ceruloplasmin** converts **Ferrous to Ferric in blood and added to Apotransferin for its transport.**

- **Thus Copper has role in Iron metabolism.**
- **Copper deficiency affects the function of Ceruloplasmin**

- **Low Ceruloplasmin levels affects Iron Metabolism:**
  - **Transport of Iron**
  - **Storage of Iron**
  - **Utilization of Iron**
  - **Heme Biosynthesis**

- Copper helps in **maintaining Myelin Sheaths of Nerve Fibers**
- **Role in development of Nervous system**

- Recently found out **Copper helps to protect the Heart**
- **By increasing HDL activity** (Scavenging Action-Reverse Transport Of Cholesterol)
- **Reduces risk of Atherosclerosis.**

- **Copper** is necessary for the **biosynthesis of:**
  - **Phospholipids**
  - **Melanin** –Skin and hair pigment

Excretion Of Copper

- Normally **85-99 %** of ingested Copper is **excreted through feces via bile**
- Remaining **1-15%** **may get excreted through Urine**.

Disorders Associated To Copper Metabolism

Deficiency Of Copper

- **Deficiency of Copper consequently lowers:**
  - **Saturation of Transferrin**
  - **Ferritin Levels**
  - **Hb concentration**
  - **Oxygen supply to tissues**
  - **ATP production in body**

Deficiency Of Copper

- **Deficiency of Copper in body directly** and **indirectly affects**:
  - –Iron Metabolism
  - –Heme Biosynthesis
  - –Leads to Iron deficiency Anemia
  - –Melanin Biosynthesis
  - –Collagen Biosynthesis

Copper Deficiency Manifestations

- Bone disorders
  - **Thin Cortices**
  - **Deficient Trabeculae**
  - **Wide Epiphyses**

- Weakness ,Weight Loss
- Atropy of Myocardium
- Demyelination
- Non Coordinated movements

Menkes Disease

Kinky /Steel Hair Syndrome

A Copper Deficiency Disorder

- **Menkes Disease is associated to Copper Metabolism.**
- It is **inherited X linked disorder affects male only.**

Biochemical Defects

- **Defects in intestinal Copper absorption.**

- Leads to **Copper deficiency in human body.**

- Due to **absence of Copper binding ATPase**

- **Defective Transport of Copper across the Serosa of mucosal cell membrane.**

- **In Menkes Disease** the **serum and Urine Copper levels are markedly decreased**.

- Copper deficiency **affects the Melanin biosynthesis**.
- Causes **hypopigmentation of Skin and hair**
- **Leads to greying of hair**
- **Flag type of hair growth** (alternate grey and white patches on hair)

Clinical Manifestations Of Cu Deficiency

- Iron Deficiency Anemia
- Depigmentation of hair
- Mental Retardation
- Abnormal Bone formation
- Susceptible to Infections.

Copper Toxicity Disorder

Wilsons Disease

Hepatolenticular Degeneration

Wilsons Disease

- Wilsons Disease is an **inherited disorder** associated to **Copper metabolism.**

Inheritance

- Wilsons Disease is inherited as **Autosomal Recessive**.

Incidence

- Incidence of Wilsons Disease is **1 in 50,000 of live births.**

Biochemical Defect

- Gene present on **Chromosome 13**
- **Encoding for Copper binding ATPase /ATP 7B Gene** in cells is defective

- Which **affects the normal excretion of Copper, through bile out from Liver cells.**

- **Copper is not excreted through bile.**

- In Wilson disease, the **Copper builds up in toxic levels in Liver**,

- Liver releases the **copper directly into blood stream**.

- In Wilsons disease due to high toxic levels of Copper in Liver
- There occurs **defect in incorporation of Copper into Apoceruloplasmin to form Ceruloplasmin**.

- Thus in Wilsons disease the **Copper atoms are underutilized**

- **Not incorporated into Apoceruloplasmin to form Ceruloplasmin**.

- **Wilsons disease** has **low Ceruloplasmin levels in blood** which **affects its Ferroxidase activity.**

- In Wisons disease **due to low Ferroxidase activity of Ceruloplasmin**

- The **Iron transport and Storage is indirectly affected.**

- **In Wilsons disease** the **unutilized Copper liberated out from damaged hepatocytes**

- **Copper is markedly excreted out through Urine.**

Clinical Manifestations

- Due to retention of Copper in functional organs like Liver ,Brain ,Kidneys and Eyes.

- In Wilsons disease following manifestations are noted.

- Accumulation of toxic levels of Copper in hepatocytes

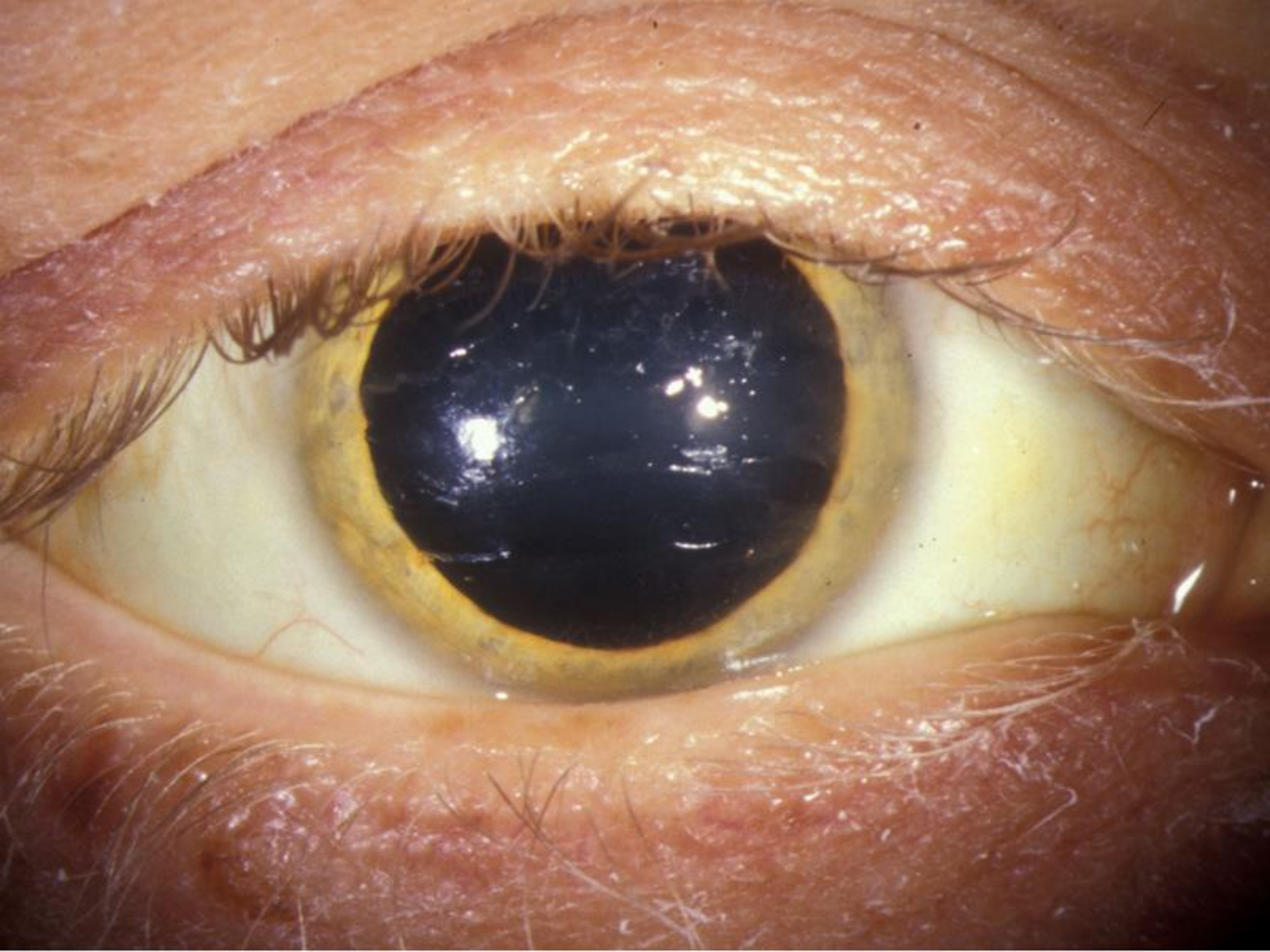
- Leads to hepatocellular degeneration and Liver Cirrhosis.

- **In Wilsons disease Copper is also deposited in brain basal ganglia**
- **Leads to lenticular degeneration and neurological symptoms.**

- **Copper deposits in Kidneys**
- **Leads to defect in renal tubular reabsorption leading to Aminoaciduria.**

- **Copper deposition in Descemets membrane** of the **eyes ,around cornea.**

- Causes a **golden brown ,yellow or green ring round the Cornea** termed as **Kayser Fleischer Ring.**



Wilsons Disease Treatment

- **Penicillamine injection Chelates the Copper**
- **Remove** the **Copper deposited in tissues and excreted out.**

- Sometimes **Zinc is used therapeutically** in Wilsons disease
- As **Zn decreases Copper absorption.**

Copper Toxicity Manifestations

- Diarrhea
- **Blue-Green Discoloration of Saliva**
- Hemolysis
- Hemoglobinuria
- Renal Failure
- Proteinuria

Zinc Metabolism

Zinc

- Zinc is an **important trace element** of human body.

- Zinc is **mainly intracellular element**.

RDA of Zinc

- Adults= **10-15 mg/day**
- Pregnant and Lactating **Women=25 mg/day**

Dietary Sources Of Zinc

- Meat
- Fish
- Eggs
- Milk
- Legumes
- Pulses
- Spinach
- Lettuce
- Yeast Cells
- Beans
- Nuts

Absorption Of Zinc

- Only **small percentage of dietary Zinc is absorbed**

- From **duodenal and ileal part of small intestine**.

- **Zn absorption is facilitated by**
- A low molecular weight **Zinc binding factor produced and secreted by Pancreas**.

- **Zn absorption is interfered with**
- **High amounts of dietary Ca, P and Phytates.**

Body Distribution Of Zinc

- The **total content of Zinc in adult** human body **is 1.5 -2 gm**.
- **high concentrations of Zinc in Prostate and Skin** (80-100 mg/100 gm).
- **Bones and teeth** contains moderate amounts of Zinc.
- **Very low** content in **Brain and Lungs.**

Zinc In Blood

- Blood Zinc Levels **120-140 μg/100ml**
- **Zinc is associated with Albumin** in blood.

Biochemical Functions Of Zinc

- Zinc **serves as inorganic cofactor for certain Enzymes**

- **Zinc containing Enzymes:**
  - **Alcohol Dehydrogenase**
  - **Alkaline Phosphatase**
  - **ALA Dehydratase**

- **Carbonic Anhydrase**
- **Carboxy Peptidase**
- **Super Oxide Dismutase-Zn**
- **LDH**
- **DNA and RNA Polymerase**

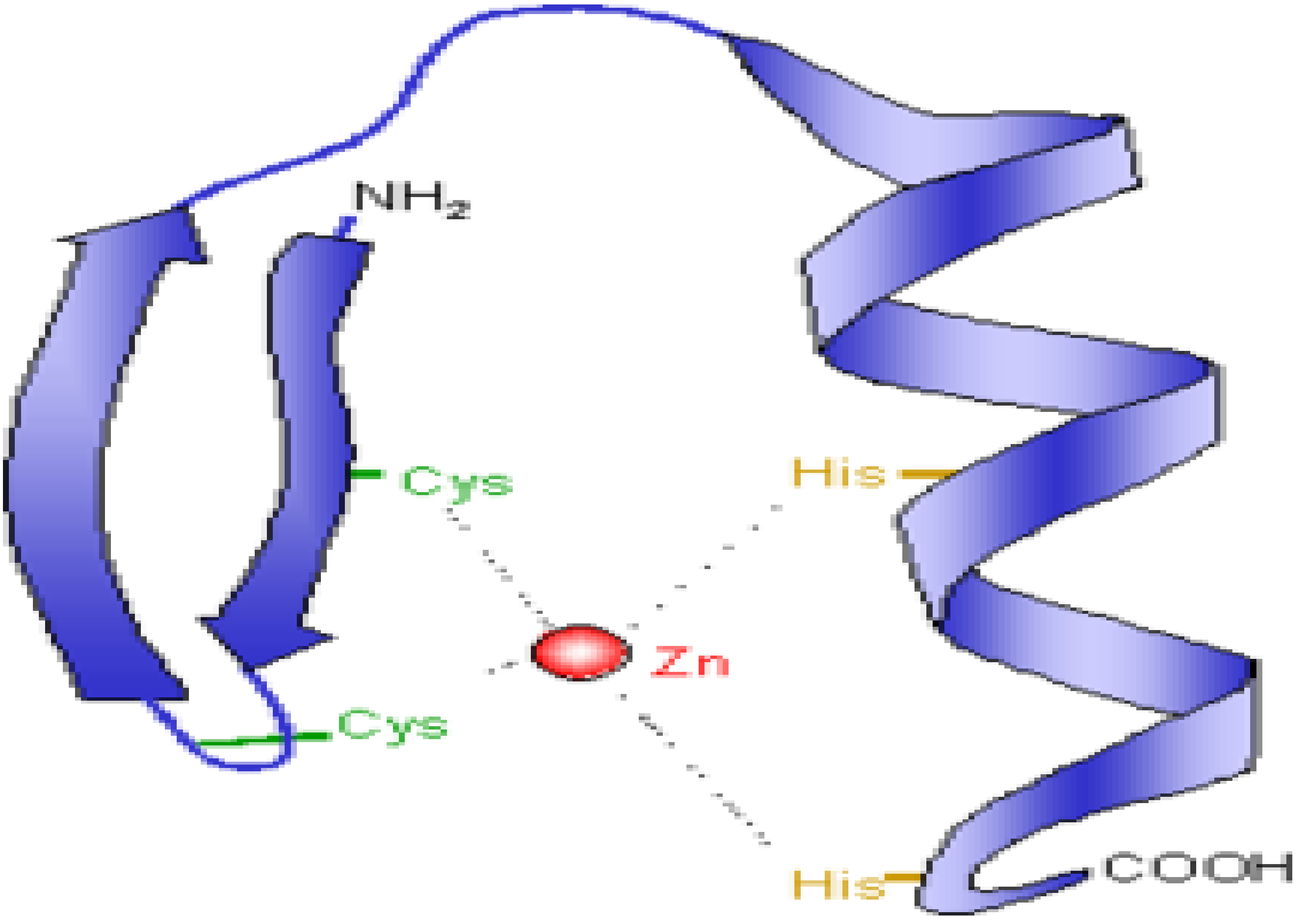
- **Zinc is required** for the **storage and secretion of Insulin hormone**
- From **the Beta cells of Islets of Langerhans of Pancreas.**

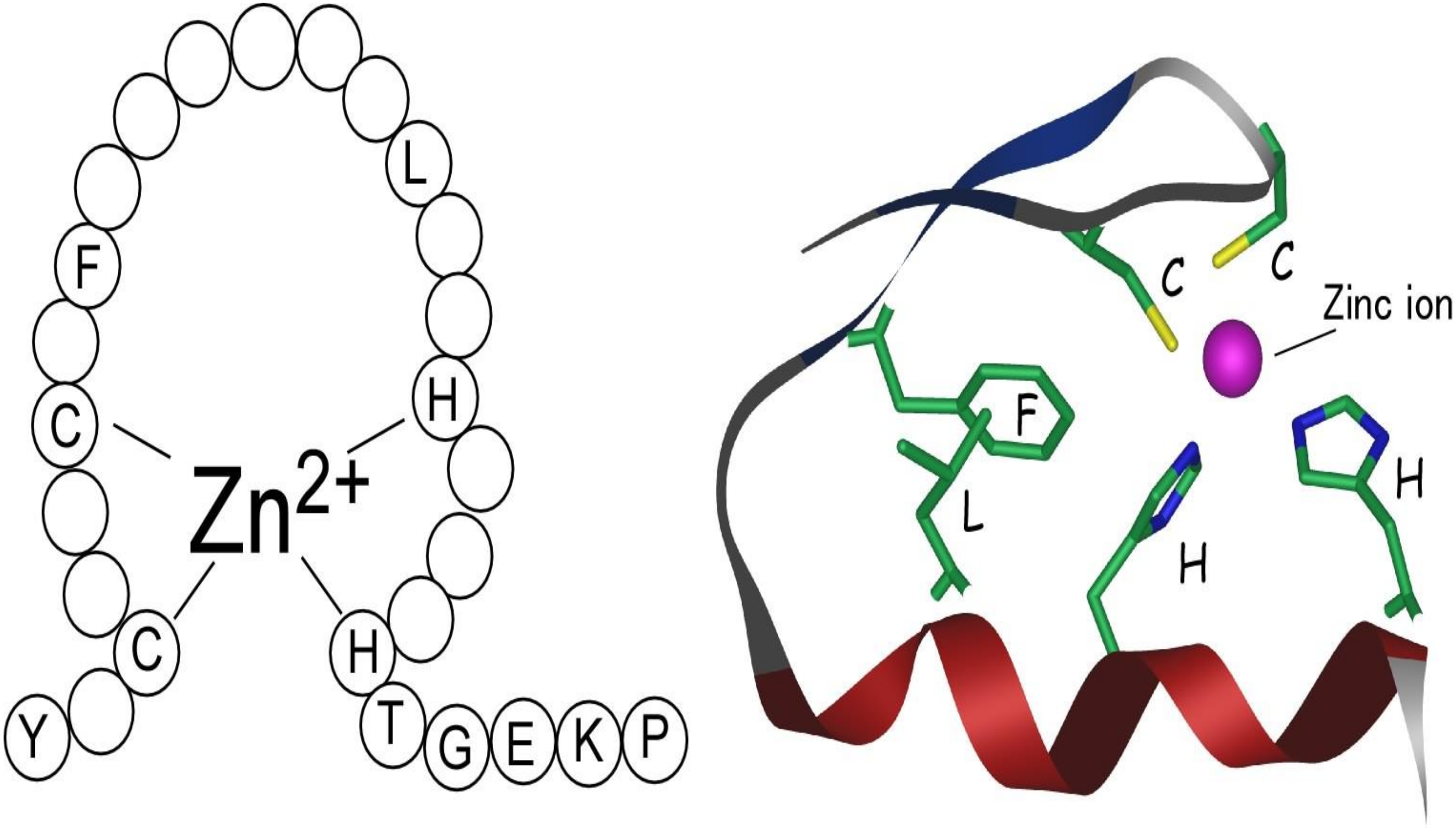
- Zinc has **role in wound healing by promoting epithelialization.**

- The **Salivary taste Protein "Gustin " contains Zn.**

- Zinc has **role in growth and reproduction** of human beings.

- Zinc **binds to regulatory** Proteins of DNA **and**
- **Involve in the control of Transcription (Zinc Finger Motif).**


NH2
Cys
His
Zn
Cys
His
COOH



Structure of C2H2 zinc finger

(C, cysteine; H, histidine)

- Zinc helps in biosynthesis of **Retinol binding Protein**.
- Thus Zinc is necessary to maintain **normal levels of Retinol(Vitamin A) in blood.**

Excretion Of Zinc

- A normal healthy body looses **9 mg of Zinc through Feces and 0.5 mg through Urine.**
- **Trace amount of Zn is lost in sweat.**
- **0.5 mg of Zn is retained in the body.**

Disorders And Manifestations Of Zinc

Zinc Deficiency Manifestations

- Poor Wound Healing
- Lesions of Skin
- Hyperkeratosis
- Dermatitis

- Alopecia
- Impaired Spermatogenesis
- Impaired Macrophage Function
- Depression ,Dementia and Other Neuropsychiatric Complications.

Achrodermatitis Enteropathica

- This is a **rare inherited disorder of Zn metabolism.**
- It is a **autosomal recessive disorder.**

Biochemical Defect

- **Defect In Zinc absorption from GIT**
- Leads to **Zinc deficiency in human body.**

Clinical Manifestations

- **Achrodermatitis- Inflammation around mouth ,nose, fingers (Dermatological Disorder)**
- GIT disturbances-Diarrhea
- Neuropsychiatric features

- Ophthalmological dysfunctions
- Growth Retardation.
- Hypogonadism
- Alopecia

Secondary Causes Of Zinc Deficiency

- Chronic Alcoholism
- Uncontrolled Diabetes mellitus.

Zinc Toxicity

- Zinc Toxicity is manifested
- When dosage of **Zn is more than 1000 mg/day**.

Causes Of Zinc Toxicity

- Zinc toxicity is **commonly noted in Welders who may inhale fumes of Zinc Oxide.**
- Many **Rat poisons contain Zn compounds** ,ingestion of it leads to Zn toxicity.

Manifestations Of Zn Toxicity

- Chronic toxicity of Zn produces Gastric Ulcer
- Pancreatitis
- Nausea ,Vomiting
- Pulmonary Fibrosis

Acute Zinc Manifestations

- Fever
- Excessive Salivation
- Headache
- Anemia
- Leukocytosis

Therapeutic Value Of Zinc

- Recent evidences has proved Zinc therapy **may reduces Atherosclerosis.**
- Administration of 3.4 mg of elemental Zn /day has **Significantly reduced serum LDL Cholesterol.**

- Prevents **Aortic wall Cholesterol deposition**
- **Prevent Platelet adhesion**
- **Increased Fibrinolytic activity.**

- **Acute fall in Zinc** is **noted on 3rd or 4th day of Myocardial Infarction**.

Fluorine Metabolism

Fluorine

- Fluorine is a **trace element**
- important in **preventing tooth caries and decay.**

RDA Of Fluorine

- **Safe limit of Fluorine is 1ppm/day**

- **1ppm= 1mg/10,000 ml**

Dietary Sources Of Fluoride

- **Drinking Water is the main source**
- **Fluoride Tooth paste**
- Tea
- Fishes
- Jawar

Absorption Of Fluoride

- The dietary soluble forms of Fluorides are absorbed by
- **Simple diffusion from intestine**.

Body Distribution OF Fluoride

- Fluoride in body is **mainly present in bones and teeth**.

- The **blood contains ionized form of Fluoride=10-20 µg%.**

Biochemical Functions Of Fluoride

- Fluorine **in trace amounts** help in **teeth development and prevent dental caries**
- By **hardening of dental enamel and maintaining Fluoroapetite**

(Calcium Fluoride).

- **Fluoroapetite** makes:
  - **Tooth surface strong**
  - **More resistant to plaque**
  - **No bacterial attack**
  - **Prevention of tooth decay**

- **Fluorine** has **role in bone development**

- **Which Prevent old age Osteoporosis.**

- **Fluoride is an inhibitor of Enzyme Enolase of Glycolysis (Antiglycolytic agent)**

- **Sodium Fluoride** is content of sugar bulb/**grey vacutainer**
- **Used for blood collection for Glucose estimation.**

Excretion Of Fluoride

- Fluorides are mainly **excreted through Urine.**

Disorders Of Fluorine Metabolism

Deficiency Of Fluorine

- Intake of **Fluorine** **less than 0.5 ppm in Children**
- May lead to Fluorine deficiency
- **Fluorine deficiency directly affects the health of teeth and bones.**

- **In Fluorine deficient persons.** the **Fluorapatite is not formed and maintained on the enamel of teeth**
- These teeth are **susceptible to acid produced by bacterial action on foods.**

- In cases of **low Fluoroapatite**
  - **Enamel is removed by acid**
  - **Dentine pulp is exposed**
  - **Leads to plaque formation**
  - **Inflammation , tooth ache/decay**

Toxicity Of Fluorine/ Fluorosis

- Intake of **Fluorine** **more than 5ppm/day** **causes Fluorosis.**

- The manifestations of **Fluorosis** are **more severe than Fluorine deficiency**.

Causes Of Fluorine Toxicity

- Drinking Fluoridinated Water
- Excessive use of Fluoride Tooth paste
- Eating Jawar

Clinical Manifestations Of Fluorosis

- **Fluorosis cause GIT upset**
  - Gastroenteritis
  - Loss of Appetite
  - Loss of Weight

- **Dental Fluorosis leads to:**
  - **Mottling of Teeth Enamel**
  - **Stratification** and **Discoloration of Teeth** **(Brown/Yellow Patches on Teeth).**

Normal

Questionable

Very mild

Mild

Moderate

Severe

Source: Fluoridation Forum Report 2002 (Page 126)

- **Fluoride levels more than 20 ppm** is very toxic
- Leads to advanced **skeletal Fluorosis /Genu valgum.**

- **Characteristic features of Skeletal Fluorosis are:**
  - **Alternate areas** of **Osteoporosis** and **Osteosclerosis** with brittle bones.

- **Bone density is increased** due to
- **Fluoride deposition in bones of limbs ,pelvis and spine.**

- Individuals are **crippled** and has **stiff joints**
- They are **unable to perform their daily routines**.

Skeletal Fluorosis

Prevention Of Fluorosis

- By **checking the Fluoride levels of drinking water of deep bore wells**

- **Reducing drinking water containing excess levels of Fluoride.**

- **Avoid use of tooth paste which are excessively fluoridinated.**
- **Restricting intake of excess Jawar.**
- Supplementation of Vitamin C.

Metabolism Of Manganese (Mn)

Manganese

- Manganese (Mn) **is a trace element**

- Mainly **found in the Nucleus**
- **In association with Nucleic acids.**

RDA For Mn

- **Adults- 2- 9 mg/day**

Dietary Sources Of Mn

- **Tea is a rich source of Mn.**
- Other sources are **Cereals,Nuts,Leafy Vegetables and Fruits.**
- **Liver an Kidney are animal food sources of Mn.**

.

- **About 3-4%** of dietary Mn is **normally absorbed in Intestine.**

- **Dietary Calcium , Phosphorous and Iron may inhibit Mn absorption.**

Body Distribution Of Mn

- The **total body content** of Mn is **about 15 mg**
- **Liver and Kidney are rich in Mn**
- The **blood Mn levels 4-20 µg%.**

- Transmagnin a Beta 1 Globulin protein.

- Transports Mn in blood

Biochemical Functions Of Mn

- **Mn** is associated with **enzyme RNA Polymerase in nucleus and helps in transcription process.**

- **Mn serves as cofactor for following Enzymes:**
  - **Arginase (Urea Cycle)**
  - **Pyruvate Carboxylase (Pyr to OAA)**
  - **IDH (TCA Cycle)**

- SOD-Mn (Mitochondrial)
- Peptidase
- Succinate Dehydrogenase

- Mn is **associated with SOD Antioxidant activity**

- Thus **Mn has an antioxidant function and prevent Lipid peroxidation**

- Mn plays important role in **Glycoprotein and Mucoprotein biosynthesis**.
- Mn is necessary for **Cholesterol and Hemoglobin biosynthesis**.

- Mn is also required for the **Bone formation and normal function of nervous system.**

Excretion Of Mn

- Mn is **excreted through bile and Pancreatic juice**.

Deficiency Of Mn

- Growth retardation
- Skeletal Deformities (Defective Chondritin SO4)
- Increased ALP levels
- Functional activity of Beta cells to produce Insulin diminished
- Severe deficiency may lead to sterility.

Manifestations Of Mn Toxicity

- Mn toxicity leads to **Psychotic and Parkinsonism like symptoms**.

Molybdenum Metabolism

Molybdenum

- Molybdenum **Trace element**
- Dietary requirement of Mo in **Adults is 0.5 mg/day**
- For **Children 0.3 mg/day**

Dietary Sources OF Mo

- **Cereals and Legumes** are rich sources of Mo.
- **Liver** is also rich in Mo.

Absorption Of Mo

- Mo is **absorbed from the intestine.**
- **Higher levels of Mo in food will impair the absorption of Copper.**

Body Distribution Of Mo

- The content of Mo in human body is very little .
- It is **mainly present in bones to smaller extent in Liver and Kidneys.**

Biochemical Functions

- **Mo is constituent of the Enzymes.**
  - **Xanthine Oxidase**

    (Purine Catabolism)
  - Sulfite Oxidase
  - Aldehyde Oxidase

- Mo in Enzymatic reactions participates
- Internal electron transfer during oxido reduction.

Excretion Of Mo

- Mo is mainly excreted through **urine to small extent through feces via bile**.

Disorders Of Mo

- **Deficiency of Mo** causes **decreased Xanthine oxidase activity**
- Which **increases Xanthinuric acid and decreases Uric acid excretion**

- **Molybdenosis** is a rare disorder caused by **excessive intake of Mo**.
- It manifests as impairment in **growth, diarrhea and Anemia**
- Excess Mo affects intestinal **Copper absorption**.

Selenium Metabolism

Selenium

- Selenium is a **trace element associated to antioxidant activity.**
- **RDA of Selenium in adults is 50-200μg/day**

Dietary Sources Of Selenium

- Rich sources of Selenium are **organ meat like Liver and Kidney**.
- **Sea Foods**
- **Food crops grown in Selenium rich soil**
- **Soil of Punjab and Haryana is rich in Selenium content**.

Absorption Of Selenium

- Selenium is mainly **absorbed from Duodenum**.

- Selenium is **transported bound to Plasma Proteins**.

Body Distribution Of Selenium

- Selenium is widely distributed in all tissues .
- Highest concentrations of Selenium are found **in Kidney ,Liver and Finger nails.**

- Low concentration of Se is found in **Muscles , Bones ,Blood and Adipose tissues**.

- **Blood levels of Selenium are 0.05 to 0.34 µg/ml**

Biological Forms Of Selenium

- The **termination codon UGA** is responsible for the **direct insertion** of **Seleno-Cystine**
- In **Selenium containing Enzymes** during Protein biosynthesis.
- Thus **Seleno-Cysteine** may be considered as the **21 st amino acid.**

- Biological forms of Selenium are analogues of **S containing amino acids viz**
  - **Selenomethionine**
  - **Selenocysteine**
  - **SelenoCystine**

Biochemical Functions Of Selenium (Se)

- **Selenium along with vitamin E has potent antioxidant function.**
- **Selenium has sparing effect on Vitamin E**
- **Selenium reduces Vitamin E requirement** in the body.

- **Selenium as Selenocysteine** is an essential component of **enzyme Glutathione Peroxidase**

- **Se containing Glutathione Peroxidase detoxifies toxic free radical H_2O_2** within cells.

- Thus this detoxification of H_2O_2 **protects the cells against the damage caused by H_2O_2.**

- Selenium also interacts with free radicals including Superoxide radicals.

- Se protects the cells from Lipid peroxidation of biological membranes
- This maintains structural integrity of the biomembranes

- Selenium prevents :
  - Intracellular hemolysis
  - Hepatic necrosis and muscular dystrophy.

- Selenium has **anticancer role**
- **Since it protects the body from the action of chemical Carcinogens on DNA and prevent from mutations.**

- **5’-Deiodinase enzyme** is another **Se containing enzyme** which has its **role in T3 Hormone biosynthesis**.

  (T4 to T3 transformation).

- **Selenium is necessary for normal development of Spermatozoa.**

- Selenium **has affinity for Hg^{+2} and Cd ions**
- It interacts with them and
- **protect the body from toxic action of heavy metals atoms**.

Excretion Of Selenium

- Main route **of Selenium excretion is through Urine**

- Very **small amount of Se excreted through feces and expired air.**

Disorders Associated
To
Selenium Metabolism

Selenium Deficiency Disorders

Keshans Disease/ Cardiomyopathy

- This Selenium deficiency disorder was first reported in –**Keshan a country of North Eastern China**.

- Mostly Childrens and Womens were **affected due to low dietary intake of Selenium**.

Clinical Manifestations

- Acute or Chronic **Cardiac enlargement**
- Arrhythmia
- E.C.G Changes
- Cardiomyopathy **(Multifocal Myocardial Necrosis)**

Treatment

- **Supplementation of Sodium Selenite**
- Is **highly effective in Prophylaxis /prevention** and **treatment of Keshans disease**.

Kashin Beck Disease (Osteoarthritis)

- Selenium Deficiency affects **mostly children's** of **age between 5 to 13 years.**

Clinical manifestations

- Severe enlargement and **dysfunctions of the joints**.
- Shortens fingers and long bones.
- **Growth retardation**
- Degenerative Osteoarthritis

Treatment

- Supplementing **20 to 120 µg/day of Selenium.**

Selenium Toxicity Disorders

Selenosis

- **Toxic doses (900 µg/day) of Selenium may lead to Selenosis .**

- Early hall mark of Selenium toxicity is **garlicky odor in breath.**

- Due to exhalation of **Dimethyl Selenide.**

Causes of Selenosis

- Workers working in **electronic ,glass and paint industries suffer from Selenosis.**

Manifestations Of Selenosis

- Chronic Dermatitis
- Loss of hair
- Brittle nails
- Diarrhea
- Weight loss

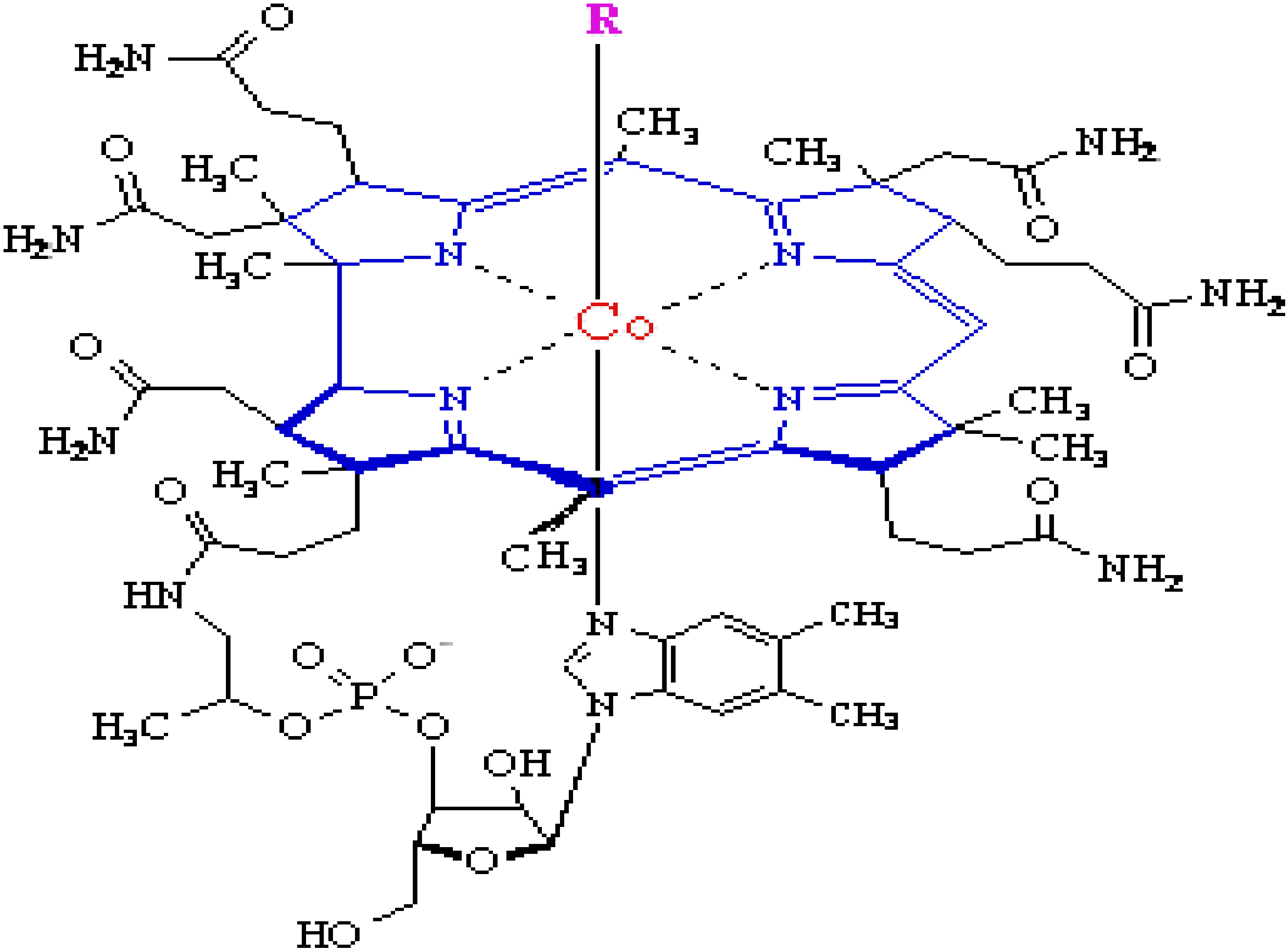
Cobalt Metabolism

Cobalt

- Cobalt is the metal atom an **essential trace element**.

- Cobalt **forms an integral parts of Vitamin B12.**

- Cobalt is a component of **Corrin ring system**.
- Corrin Ring is an internal component of **Cyanocobalamin/Vitamin B12**


R
Co
H2N
O
NH2
CH3
H3C
N
HN
P
O⁻
OH
HO

RDA Of Cobalt

- The daily requirement of Cobalt is **5 to 8 µg/day.**

Dietary Sources Of Cobalt

- Cobalt is mainly present in animal food sources
- Co not present in vegetables.

Absorption Of Cobalt

- **70-80%** of the dietary Cobalt is **readily absorbed from the intestine.**

Body Distribution Of Cobalt

- Cobalt is **mainly stored in Liver cells.**
- **Trace amount is present in other tissues.**

Biochemical Functions

- Cobalt is the **component of Corrin Ring System of Vitamin B 12/ Cyanocobalamin**.

- In human body Cyanocobalamin is transformed to **Adenosyl Cobalamin which has Coenzyme role.**

- Vitamin B 12 is **used in DNA multiplication.**
- Cyanocobalamin has role in normal functioning of the **Brain and Nervous system.**

- Cobalt is required to maintain **normal bone marrow function. Blood formation**

- Help in **maturation of RBC's by synthesis of Erythropoietin hormone.**

- Cobalt serve as cofactor for enzyme **Glycyl-Glycine Dipeptidase** of intestinal juice.

Excretion Of Cobalt

- 65% of ingested Cobalt is excreted almost through Urine.

Disorders Of Cobalt Metabolism

- **Cobalt deficiency** in humans is a rare deficiency of Vitamin B12 **leads to Macrocytic Anemia**.

- **Cobalt toxicity** results in **overproduction of R.B.Cs causing Polycythemia.**

Chromium Metabolism

- Traces of **Chromium plays important role in Carbohydrate ,Lipid and Protein Metabolism.**

RDA Of Chromium

- **10 -100 µg/day** is RDA of Chromium for an Adult body.

Dietary Sources Of Cr

- Yeast
- Cheese
- Grains
- Cereals
- Meat
- **Food cooked in Steel vessels increases Chromium contents of food .**

Absorption

- Chromium is mainly **absorbed from small intestine.**
- It is **transported through Transferrin.**

Body Distribution Of Chromium

- Human body **contains about 6mg** of Chromium mainly **resides in Mitochondria, Microsomes** and **Cytosol** of Liver cells.
- **Blood levels of Chromium 20 µg %**

Biochemical Functions Of Chromium

- **Role of Cr in Carbohydrate Metabolism:**

- **Trivalent Cr** is known as **Glucose Tolerance Factor**
- Since Cr along with Insulin **promotes the uptake and utilization of Glucose by cells** (Cr alone is ineffective).
- **Thus Cr is true promoter of Insulin.**

- **Role of Cr In Lipid Metabolism:**

- Chromium **lowers the Serum Cholesterol levels**
- Decreases **and prevents atheromatous plaque formation in aorta**.

- **Role of Cr in Protein metabolism:**
- Cr participates in the **transport of amino acids into the cells of Liver and Heart.**

Chromium Related Disorders

- Deficiency of Cr causes **disturbances in Carbohydrates ,Lipid and Protein metabolism**
- **Causes impaired Glucose tolerance.**

Chromium Toxicity:

- **Hexavalent Cr is more toxic than Trivalent Cr.**
- Cr toxicity **increases lung cancer ,Liver and Kidney damage.**

List Of Minerals With Antioxidant Activity

- Selenium
- Copper
- Zinc
- Manganese

List Of Minerals
With Neuro Muscular Activity

- Calcium
- Sodium
- Potassium
- Chloride

List OF Minerals With Bone Involvement

- Calcium
- Phosphorous
- Magnesium
- Copper
- Fluorine

Elements of Human Body

TABLE 2–1. Elements of the Human Body

Element	Symbol	Mass in 70-Kg Human	Comments
Organic matter and water			
Oxygen	O	45.5 kg	Found in organic chemicals and water
Carbon	C	12.6 kg	Found in organic chemicals
Hydrogen	H	7.0 kg	Found in organic chemicals and water
Nitrogen	N	2.1 kg	Found in nucleic acids and amino acids
Phosphorous	P	0.7 kg	Found in nucleic acids and many metabolites; constituent of bones and teeth
Sulfur	S	0.175 kg	Found in proteins and connective tissue
Abundant minerals			
Calcium	Ca	1050 g	Constituent of bones and teeth; intracellular second messenger; triggers exocytosis and muscle contraction
Potassium	K	245 g	Principal intracellular cation; obligatory loss of 40 mEq/d in urine
Sodium	Na	105 g	Principal extracellular cation
Chloride	Cl	105 g	Major extracellular anion; activates amylase
Magnesium	Mg	35 g	Cosubstrate for ATP and other nucleotide reactants; a calcium antagonist
Fluoride	F	8 g	Increases hardness of bones and teeth; excess produces dental fluorosis
Trace minerals			
Iron	Fe	3000 mg	Found in hemoglobin, myoglobin, cytochromes, iron-sulfur proteins; deficiency leads to a microcytic anemia
Zinc	Zn	2300 mg	Cofactor for carbonic anhydrase, carboxypeptidase, and cytosolic superoxide dismutase
Copper	Cu	100 mg	Component of cytochrome a, a_3 and cytosolic superoxide dismutase
Manganese	Mn	20 mg	Cofactor for mitochondrial superoxide dismutase
Cobalt	Co	5 mg	Component of vitamin B_{12}
Molybdenum	Mo	Trace	Component of xanthine dehydrogenase in purine metabolism and aldehyde oxidase in catecholamine metabolism
Iodine	I	Trace	Required for production of thyroid hormones T_4 and T_3; hyperthyroidism is treated with radioiodine
Selenium	Se	Trace	Component of glutathione peroxidase.

Questions

Long Essays

- Q.1.Enumerate the Principle elements of our body? **Describe the calcium metabolism** with respect to dietary rich sources, RDA, factors affecting its absorption, distribution, functional role, excretion & disorders associated with it.

- Q.2.Describe the **Phosphorous metabolism** in details with respect to dietary sources, RDA, absorption, functions & disorders associated with it.

- Q.3.Enumerate the **body electrolytes**. Describe the role of Na, K & Cl in the body.
- Q.4.Name the **trace elements in the body.** Describe in details of **Iron metabolism**.

- Q.5.Describe the role of trace elements in the body with respect to Cu, I_2, Fl, Mn, Se, Zn & Mo.
- Q.6.Describe the Magnesium metabolism in details.

- **Short Notes**
  - Factors affecting calcium absorption.
  - Homeostasis of calcium/Regulation of serum calcium.
  - Condition of Hypercalcemia & Hypocalcemia.
  - Role of Calcitriol in calcium metabolism.
  - Tetany.

- Transferrin & Ferritin/Transport & storage of Iron.
- Mucosal Block Theory/Absorption of Iron.
- Differences between Ferritin and Hemosiderin.
- Nutritional Hemosiderosis/Bantu's Siderosis.

– Hemochromatosis/Bronze Diabetes.
– Iron deficiency Anemia-cause & clinical manifestations.
– Wilson's disease

- Menke’s disease.
- Goiter
- Flurosis/Genu Valgum
- Selenosis/Selenium Toxicity
- Deficiency of Zinc
- Conditions of Hypernatremia & Hyponatremia.
- Causes of Hyperkalemia & Hypokalemia

- Clinical significance of Phosphorous.
- Give the list of Zn, Mg, Cu, Se, Cl, Mo requiring enzymes of human body.
- Role of Ceruloplasmin.
- Keshan’s disease
- Justify Iron is one-way element.
- How serum electrolytes are estimated? What are its normal values present in blood.

Thank you