MINERAL METABOLISM

INTRODUCTION

- Minerals are **inorganic compounds** that are required for the body as one of the nutrients.
- The inorganic elements (minerals) constitute only **small proportion** of the body weight.
- Human body needs a number of **minerals for its functioning.**

FUNCTIONS-

Minerals perform many vital functions which are essential for existence of organism-

1. Calcification of bones
2. Blood coagulation
3. Neuromuscular irritability
4. Acid-base equilibrium
5. Fluid balance
6. Osmotic regulation

CLASSIFICATION OF MINERALS

Macrominerals

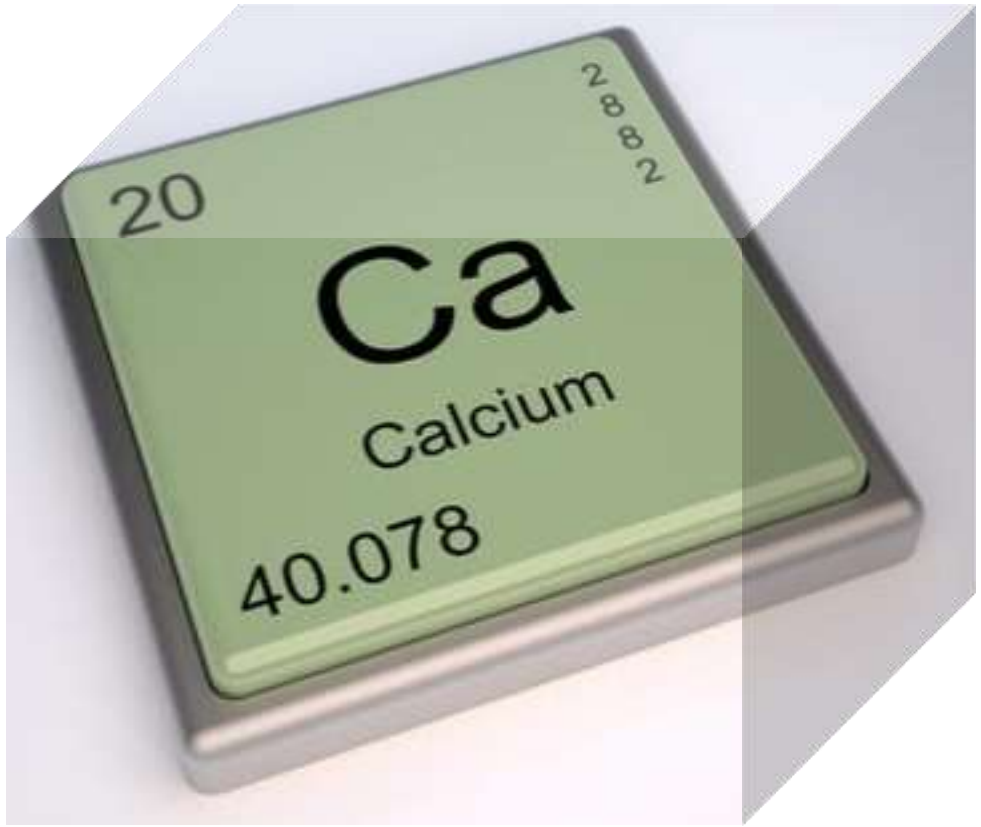
Required in excess of 100mg/day

Ca^{++}, P, S, Mg, Cl, Na, K.

Microminerals

Required in amounts less than 100mg/day

Fe, Cu, Zn, Mo, I, Fl, Cr, CO, Mn


20
2 8 8 2
Ca
Calcium
40.078

CALCIUM

OBJECTIVES

- Sources and RDA
- Metabolism of calcium
- Functions of calcium
- Regulation of plasma calcium
- Disorders of calcium metabolism

INTRODUCTION TO CALCIUM

- The most abundant mineral found in human body is **CALCIUM.**
- Calcium is essential for your body's overall nutrition and health.
- Calcium makes up approximately **2%** of your total body weight and contributes to many basic body functions, including disease prevention and absorption of other nutrients.
- Human body contain **about 1-1.5 kg of calcium**.
- **99%** of which is present in **bones , teeth** and **1%** in **extracellular fluid.**

SOURCES OF CALCIUM

- **Milk is a good source for calcium.**
- Calcium content of cow's milk is about 100 mg/100 ml.
- Egg, fish and vegetables are medium sources for calcium.
- Cereals (wheat, rice) contain only small amount of

DAILY REQUIREMENTS OF CALCIUM

Children
(1-18years)
1000mg/day

Adults
(men & women)
500-800mg/day

Pregnancy and lactation
1500mg/day

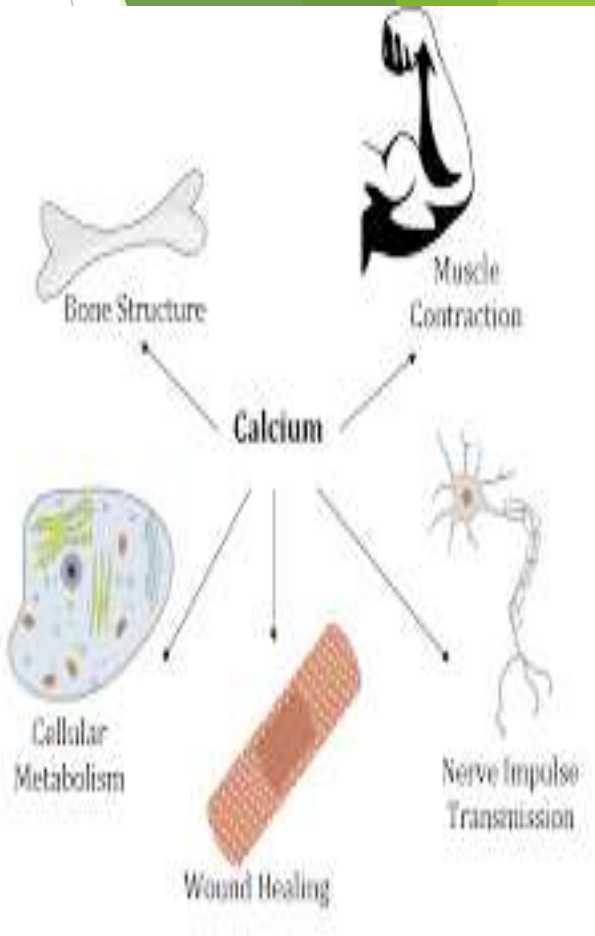
BIOCHEMICAL FUNCTIONS OF Ca^{2+}

- ***GROWTH OF BONE & TEETH-***

The bulk quantity of calcium is used for bone and teeth formation. Bones also act as **reservoir** for calcium in the body. Osteoblasts induces bone deposition and osteoclasts produce demineralization.

- ***MUSCLE CONTRACTION-***

Calcium mediates **excitation and contraction of** muscle fibers. Calcium interacts with troponin C to trigger muscle contraction. It also activates ATPase, increases the interaction between Actin and myosin.



❖ ***BLOOD COAGULATION-***

Calcium is known as **factor IV** in blood coagulation cascade.

❖ ***NERVE CONDUCTION-***

Calcium is necessary for transmission of **nerve** impulses from presynaptic to postsynaptic region.

❖ ***SECRETION OF HORMONES-***

Calcium mediates secretion of **insulin, parathyroid hormone, calcitonin, vasopressin**, etc. from the cells.

❖ ***CALCIUM AS INTRACELLULAR MESSENGER-***

Calcium and cyclic AMP are **second messengers** of different hormones Eg: Glucogan.

❖ ***ACTIVATION OF ENZYMES-***

Calcium is needed for the direct activation of enzymes, such as **LIPASE** (pancreatic), **SUCCINATE DEHYDROGENASE.**

Calmodulin is a Calcium binding regulatory protein. Calmodulin can bind with 4 calcium ions. It is part of various regulatory **kinases.**

e.g, **Pyruvate kinase** etc.

❖ ***ACTION ON HEART-***

Ca++ acts on myocardium and **prolongs systole.**

In hypercalcemia, cardiac arrest is seen in systole.

METABOLISM OF CALCIUM

ABSORPTION

20-30% of dietary calcium is **absorbed in duodenum** by active process.

FACTORS AFFECTING CALCIUM ABSORPTION

✓ ***Calcium absorption is increased by-***

1. **Calcitriol** is the active form of **vitamin D.** It increases the blood calcium and promotes Ca absorption.
2. **PTH** enhances Ca absorption through increased synthesis of Calcitirol.
3. **Lactose** promotes Ca uptake by intestinal cells.
4. **Low ph (acidic)** is favourable for Ca absorption.
5. **Lysine** and **arginine** increases Ca absorption.

FACTORS AFFECTING CALCIUM ABSORPTION

- ✓ ***Calcium absorption is decreased by-***

1. **Deficiency of vitamin D** inhibits Ca absorption.
2. **Phytates & oxalates** form insoluble salts and interfere with Ca absorption.
3. **High content of dietary phosphate** results in formation of insoluble calcium phosphate and prevent Ca uptake. **Optimum Ca:P level is between 1:2 to 2:1.**
4. **High pH (alkalic)** is unfavourable for Ca absorption.
5. **High content of dietary fiber** interferes with Ca absorbtion.

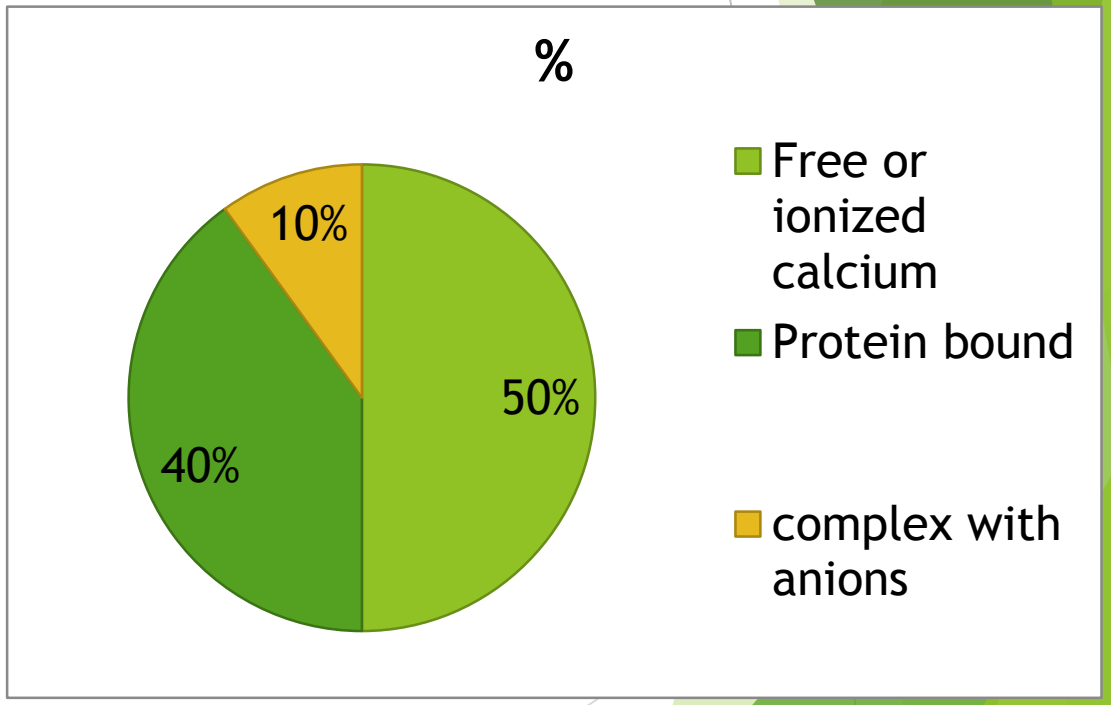
PLASMA CALCIUM

Most of the blood Ca is present on plasma whereas content of Ca in blood cell is very little.

NORMAL RANGE-

Plasma calcium **9 to 11mg/dl**

Urine calcium: **100-250 mg/day**



Calcium in plasma is of 3 types

- Ionized or free or unbound calcium
- Bound calcium
- Complexed calcium

- **Ionized or free or unbound calcium or diffusible:** **5.5 mg/dl**

  In blood, 50% of plasma calcium is free & is metabolically active.

- It is required for
  - Maintenance of nerve function
  - Membrane permeability
  - Muscle contraction
  - Hormone secretion
- **Bound calcium or non diffusible:** **4.5 mg/dl**

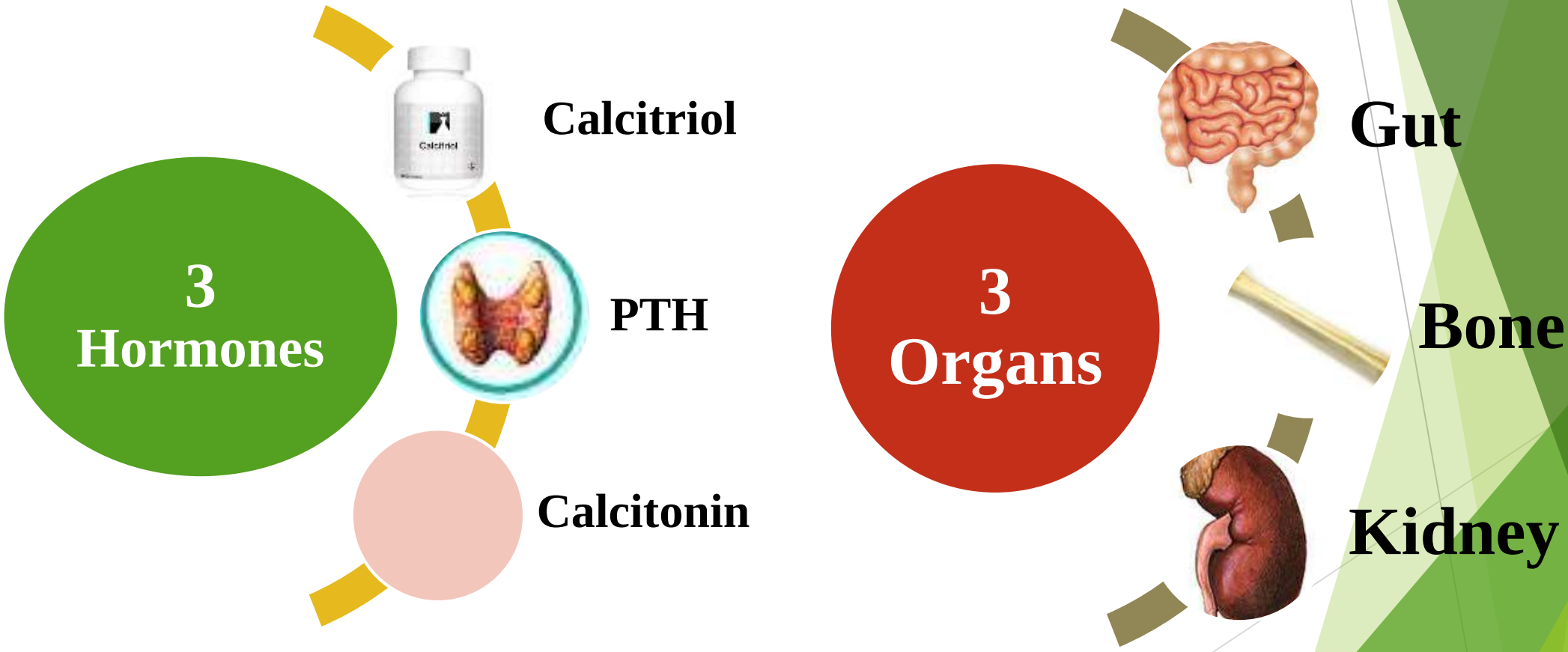
  40% of plasma calcium is bound to proteins – albumin

- **Complexed calcium:** **1 mg/dl**

  10% of plasma calcium is complexed with anions including bicarbonate, phosphate, lactate & citrate

- All the three forms of calcium in plasma remain in equilibrium with each other.

REGULATION OF PLASMA CALCIUM

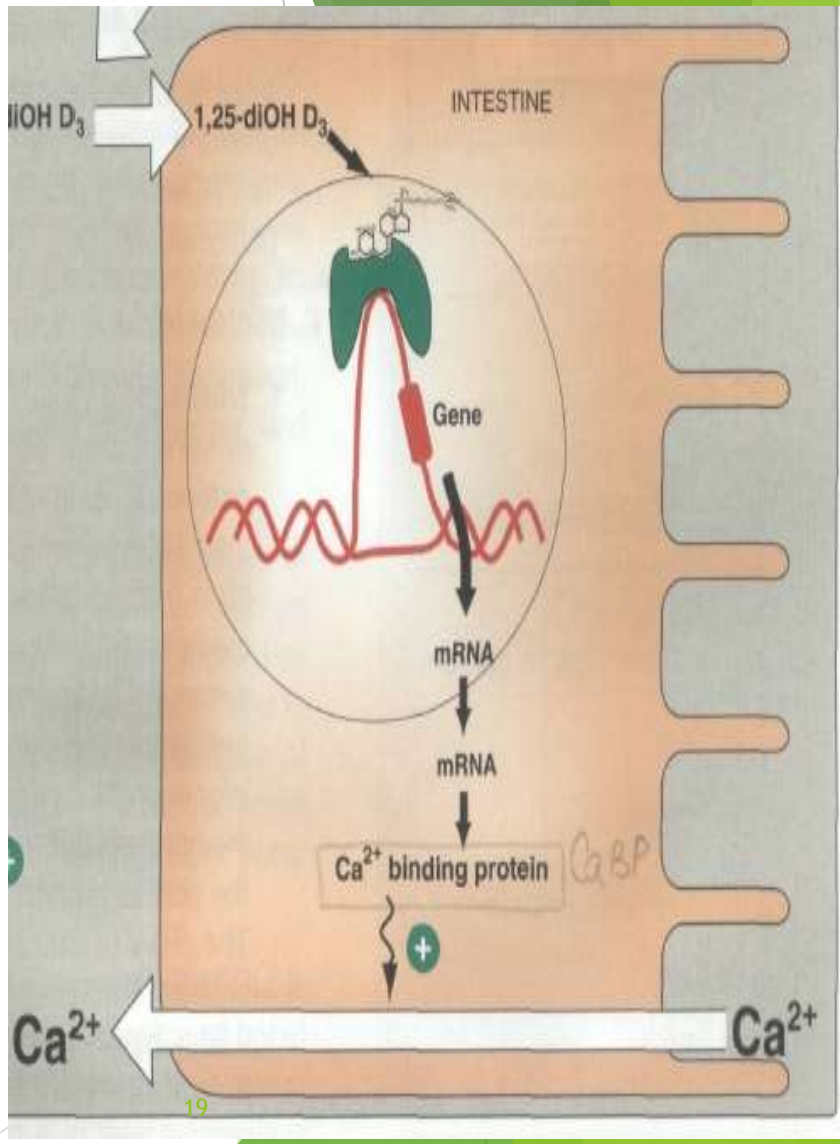


MECHANISM OF CALCIUM ABSORPTION

ROLE OF CALCITRIOL

1) On Intestine:

- **Calcitriol (dihydroxycholecalciferol)** increases intestinal absorption of Ca^{2+} & phosphate.
- **Calcitriol** enters the intestinal cell and binds to a cytoplasmic receptor.
- Complex interacts with DNA leading to the synthesis of a specific calcium binding protein.
- This protein increases calcium uptake by intestine



2) **On Bone:**

- Calcitriol (Vitamin D) is acting independently on bone. Vitamin D increases the number and activity of **osteoblasts.**
- In osteoblasts of bone, calcitriol stimulates calcium uptake for deposition as calcium phosphate.
- It also stimulates secretion of **alkaline phosphatase.**
- Due to this enzyme, calcium and phosphorus increases, leading to mineralization

3) **On Kidneys:**

- Calcitriol increases the reabsorption of calcium and phosphorus by renal tubules, therefore, both minerals are conserved.

ROLE OF PARATHYROID HORMONE

1)Action on the bone:

- PTH causes decalcification or demineralization of bone, a process carried out by osteoclasts..
- This is brought out by **pyrophosphatase & collagenase**
- These enzymes result in bone resorption.
- **Demineralization** ultimately leads to an increase in the blood Ca^{2+} level.

2) On Kidneys:

- PTH increases the Ca^{2+} reabsorption by kidney tubules
- It is most rapid action of PTH to elevate blood Ca^{2+} levels
- PTH promotes the production of calcitriol (1,25 DHCC) in the kidney

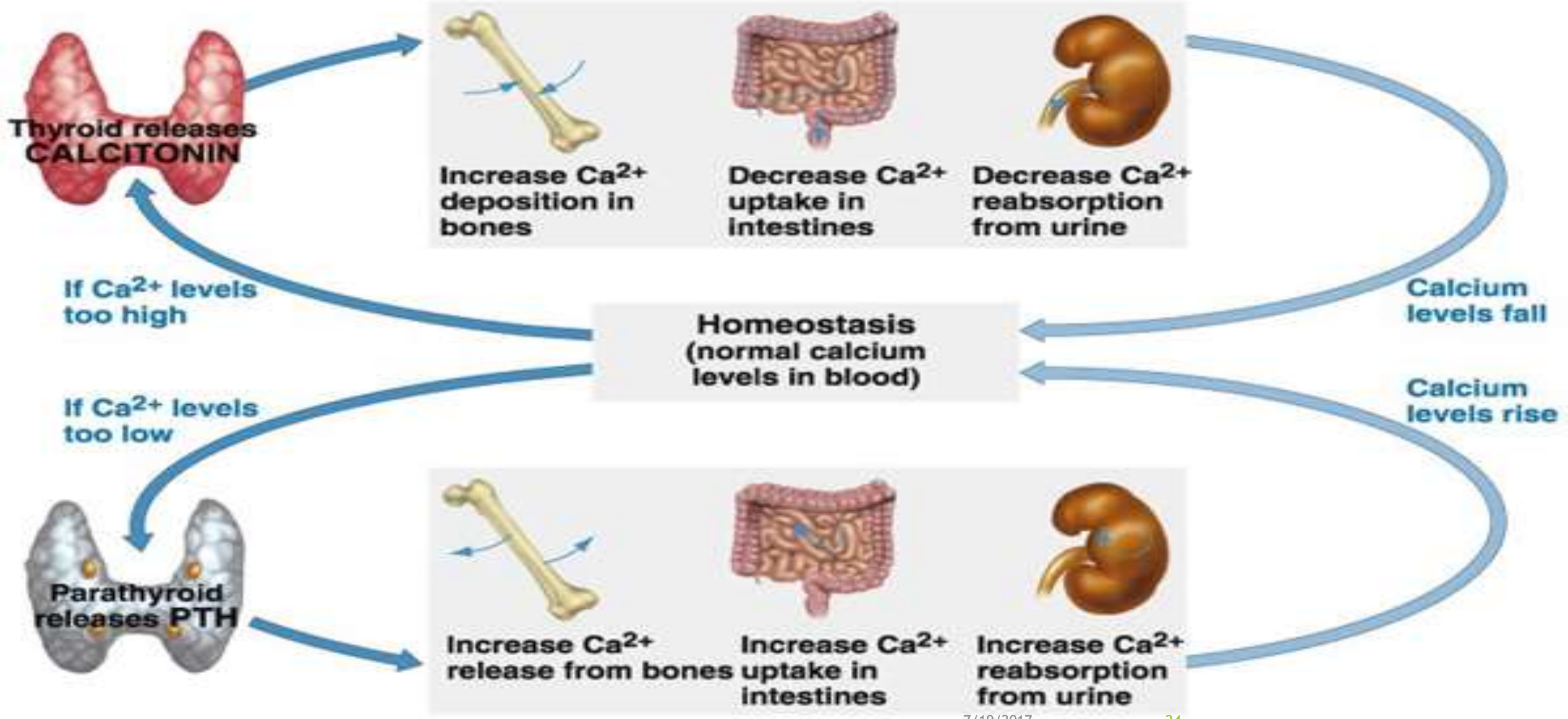
3) On Intestine:

- It increases the intestinal absorption of Ca^{2+} by promoting the synthesis of calcitriol.

ROLE OF PARATHYROID HORMONE

- Calcitonin is a **peptide** containing 32 amino acids.
- It is secreted by **parafollicular cells** of thyroid gland.
- The action of calcitonin on calcium is **opposite** to that of PTH.
- Calcitonin **promotes calcification** by increasing the activity of osteoblasts.
- Calcitonin **decreases bone resorption** & increases the excretion of Ca^{2+} into urine
- Calcitonin has a **decreases blood calcium level.**

CALCITONIN, CALCITRIOL & PTH ACT TOGETHER



EXCRETION OF CALCIUM

Stools

Unabsorbed calcium in the diet

60 – 70%

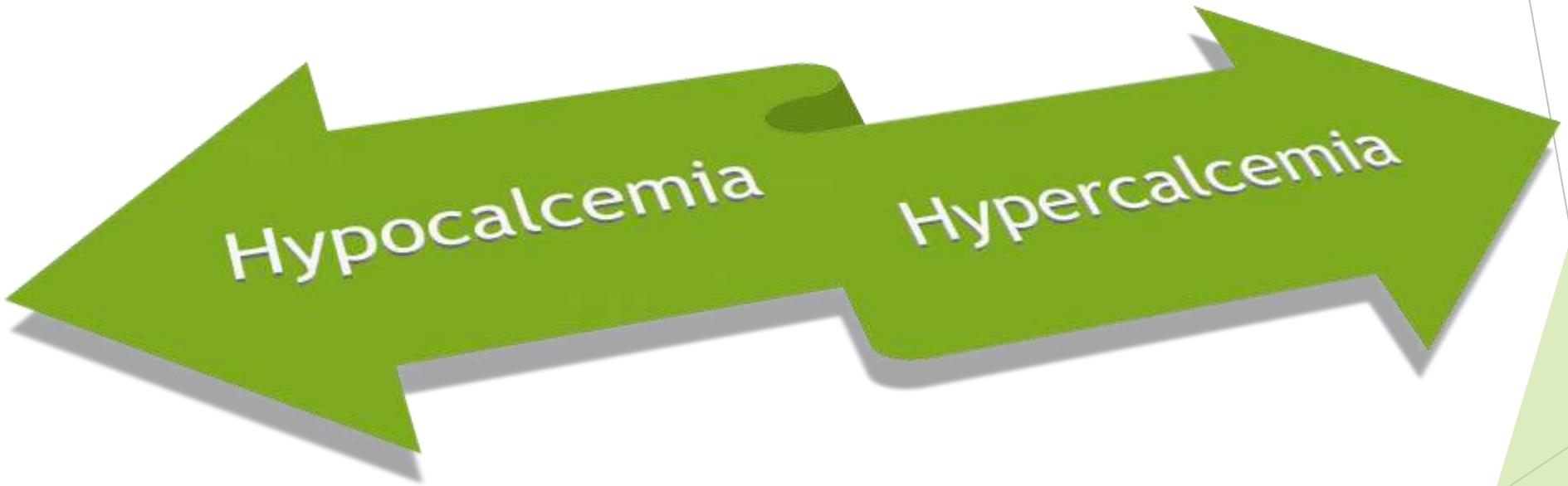
Urine

50-200mg/day

Sweat

15mg/day

DISORDERS OF CALCIUM METABOLISM



HYPOCALCEMIA

Decreased serum Ca^{2+} < 8.8 mg/dl

HYPOCALCEMIA

CAUSES

- Inadequate intake
- Impaired absorption
- Increased excretion
- Magnesium deficiency

HYPOCALCEMIA - FEATURES

Muscle cramps and tetany

- Laryngospasm (difficult to speak or breathe)
- Convulsion **(seizures)**

Cardiac arrhythmias

- Prolongation of QT interval (slow heart rate)

Cataract

- Chronic hypocalcemia

HYPOCALCEMIA - TREATMENT

Severe symptomatic cases

- Intravenous Calcium gluconate

Asymptomatic cases

- Calcium carbonate
- Vitamin D

HYPERCALCEMIA

Increased serum Ca^{2+} level >11 mg/dl

HYPERCALCEMIA

- Increased intake
- Increased absorption
- Decreased excretion
- Malignancy (Cancers that affect the bone)

HYPERCALCEMIA - FEATURES

- Metastatic calcification (accumulation of calcium other than bones or teeth)
- Neurological symptoms (Depression, confusion, inability to concentrate)
- Renal symptoms (calcification of renal tissue)
- Gastrointestinal symptoms (abdominal pain, nausea, vomiting & constipation)
- Cardiac arrhythmias

HYPERCALCEMIA - TREATMENT

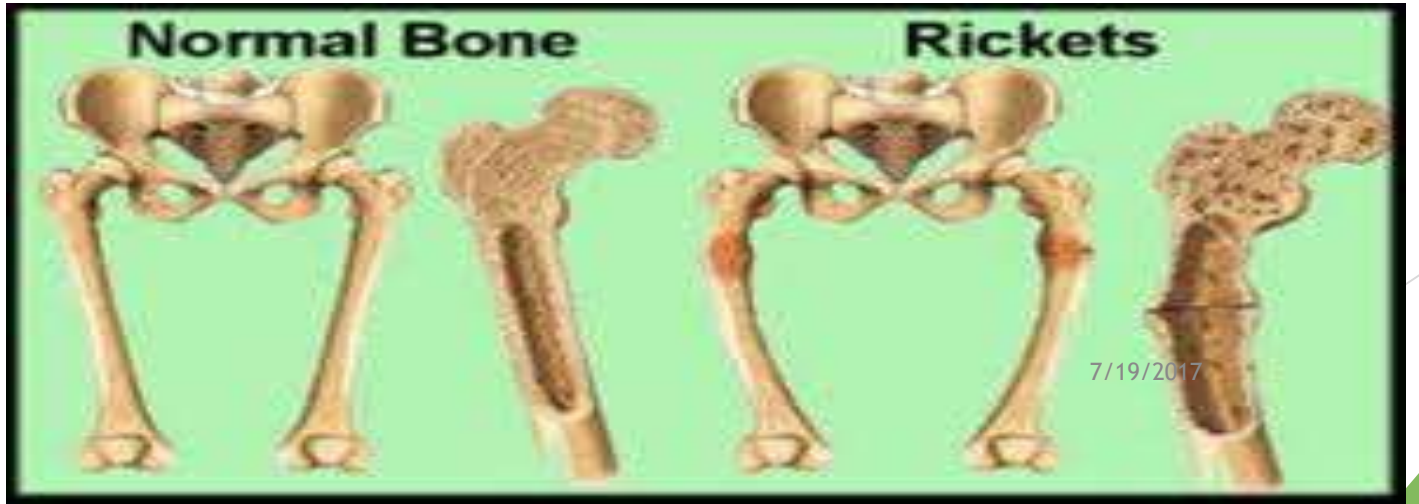
Calcimimetics- This type of drug mimics calcium circulating in the blood, so it can help control overactive parathyroid glands.

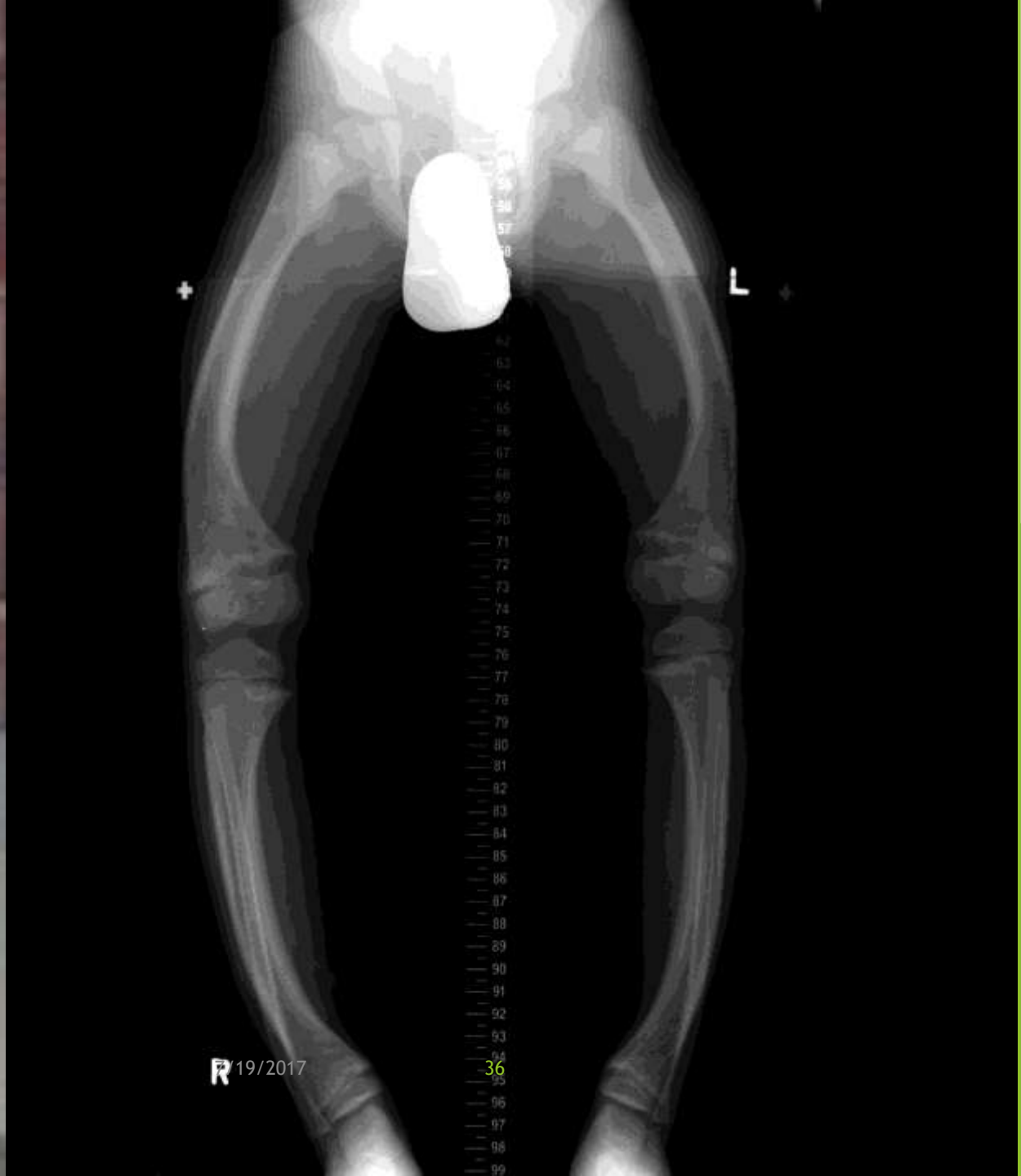
Prednisone- If hypercalcemia is caused by high levels of vitamin D, short-term use of steroid pills.

Steroids- if there is calcitriol excess

RICKETS

- Rickets is a **disorder of defective calcification of bones.**
- This may be due to a **low levels of vitamin D** in the body or due to a dietary **deficiency of Ca^{2+} & P** or both.
- The concentration of serum Ca^{2+} & P may be **low or normal**
- An increase in the activity of **alkaline phosphatase** is a characteristic feature of rickets.

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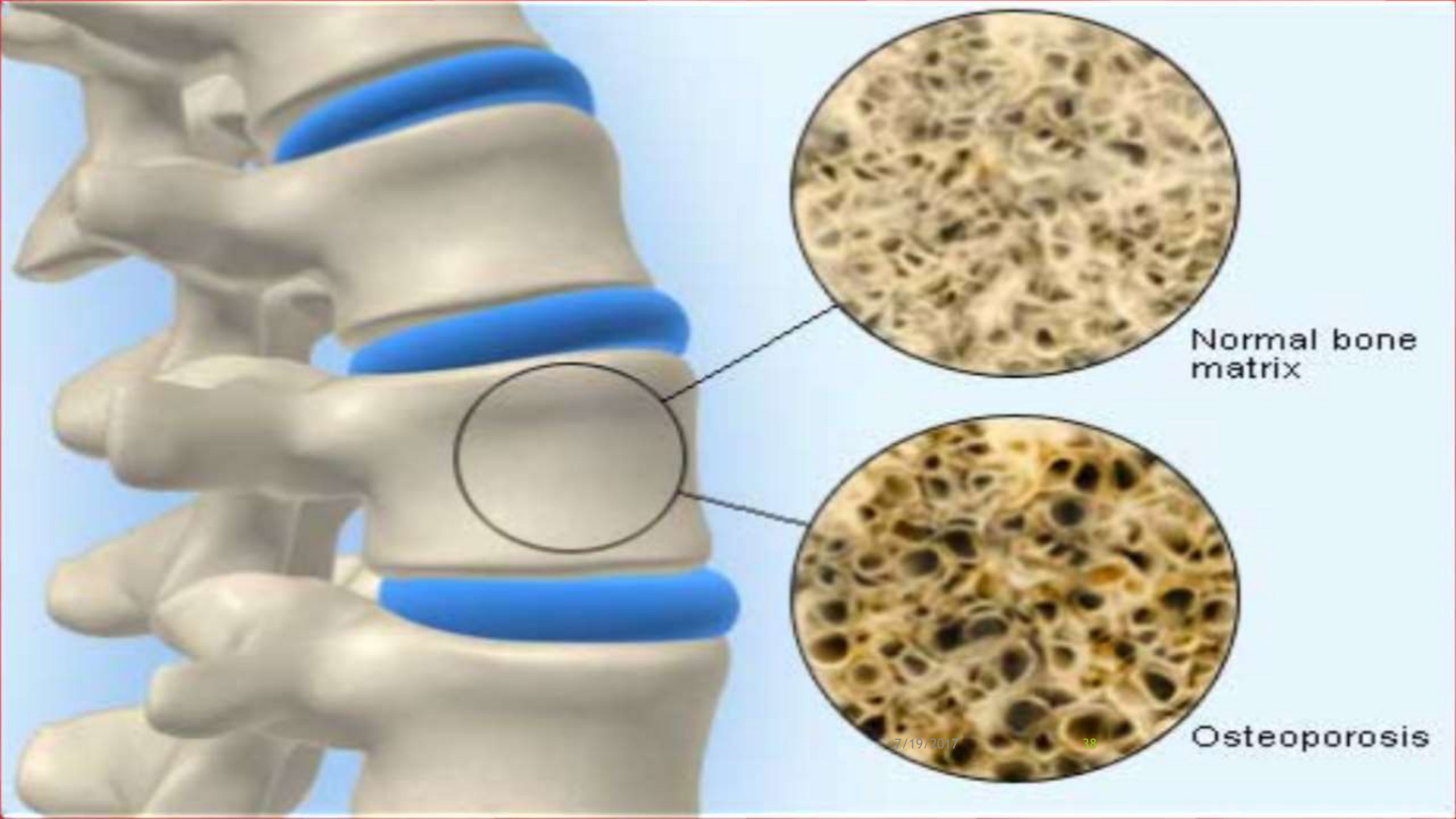
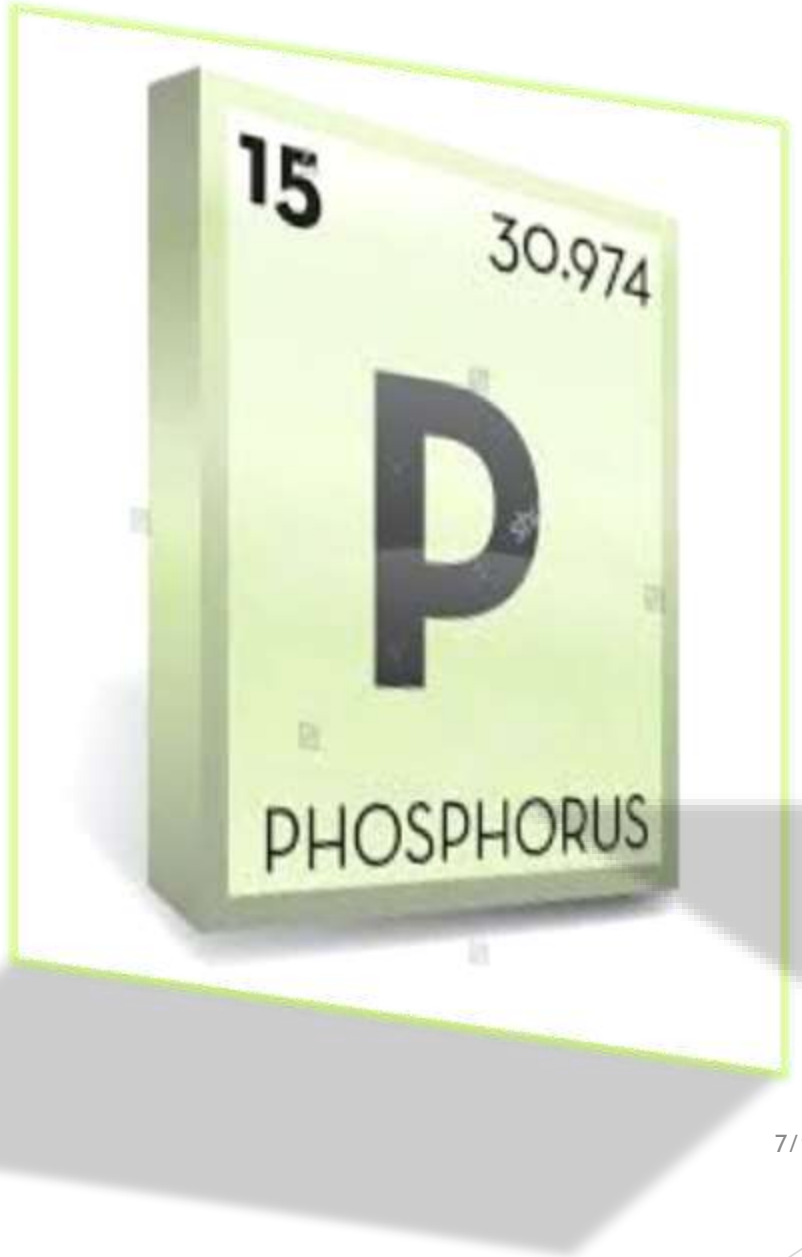
OSTEOPOROSIS

- Characterized by **demineralization of bone** resulting in the progressive loss of bone mass.
- After the age of 40-45, **Ca^{2+} absorption is reduced** & Ca^{2+} **excretion is increased**; there is a net negative balance for Ca^{2+}
- After the age of 60, osteoporosis is seen
- There is **reduced bone strength** & an **increased risk of fractures**.
- Decreased absorption of vitamin D & reduced levels of androgens/estrogens in old age are the causative factors.


Normal bone matrix
Osteoporosis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PHOSPHORUS

PHOSPHORUS

OBJECTIVES

- Sources
- RDA
- Functions of calcium
- Metabolism of calcium
- Disorders of calcium metabolism

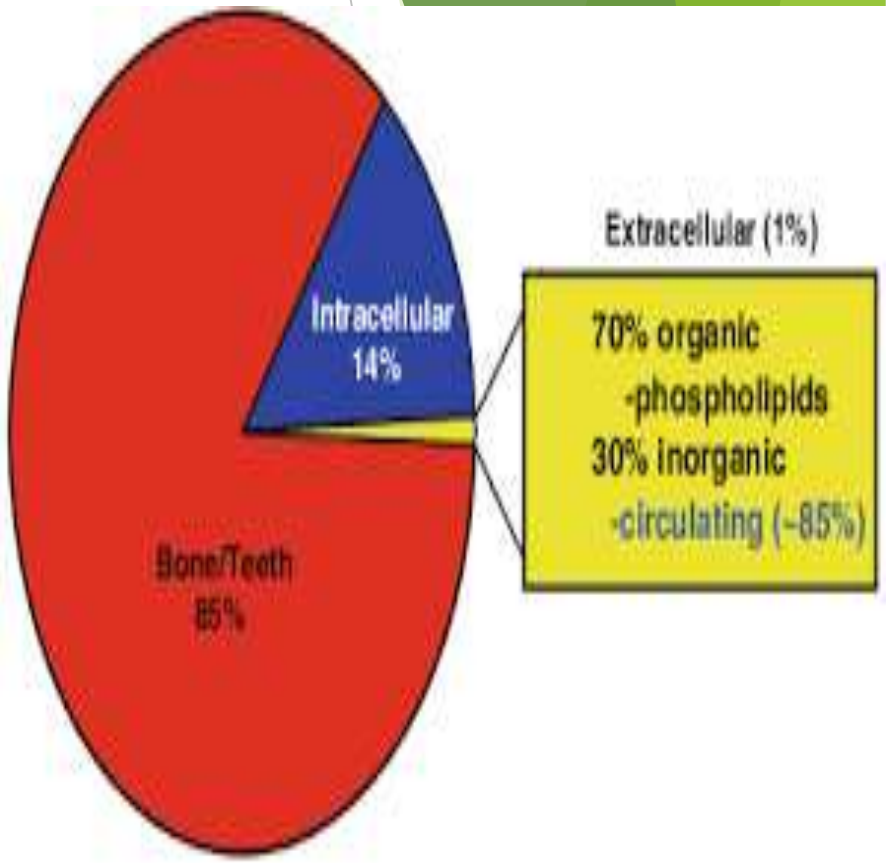
INTRODUCTION TO PHOSPHORUS

- Human body contains - 1 kg of phosphorous
- **Body distribution:**

✓ 85% of phosphorous is found in bones & teeth in combination with calcium.

✓ 14% of phosphorous is present in soft tissues, as a component of phospholipids, phosphoproteins, nucleic acids & nucleoproteins.

✓ 1% is found in ECF, as inorganic form



SOURCES OF PHOSPHORUS

- The food rich in calcium is also rich in phosphorous

  i.e. milk, cheese, beans, eggs, cereals, fish & meat

- **Milk is good source of phosphorous**

DAILY REQUIREMENTS OF PHOSPHORUS

Calcium & phosphorous are distributed in majority of natural foods in 1:1 ratio.

Children
(9-18years)
1250mg/day

Adults
(men & women)
800mg/day

Pregnancy and lactation
1200mg/day

FUNCTIONS

Formation of bone and teeth.

Production of high energy phosphate compounds such as **ATP, CTP, GTP, creatine phosphate, etc.**

Synthesis of nucleoside co-enzymes such **as NAD and NADP**.

DNA and RNA synthesis, where **phosphodiester linkages** form the backbone.

Formation of phosphate esters such as **glucose-6-phosphate, phospholipids**.

Formation of phosphoproteins, **e.g. casein**.

Activation of enzymes by phosphorylation.

Phosphate buffer system in blood. The ratio of **Na_2HPO_4 : NaH_2PO_4** in blood **is 4:1 at pH of 7.4.**

METABOLISM OF PHOSPHORUS

ABSORPTION

90% of dietary phosphorous is absorbed in **JEJUNUM**

Phosphorus absorption increased by

- Bile salts
  Acidity
  PTH and vitamin D
  Calcium

Phosphorus absorption decreased by

- High Ca: P ratio
  Alkalinity
  Magnesium and aluminium

PHOSPHORUS - DISTRIBUTION

Human body contain about 840gm of phosphorus

80% present in bone and teeth

20% in other tissue

NORMAL RANGE- Serum phosphate level **2.8-4.5mg/dl**

REGULATION OF PLASMA PHOSPHORUS

3 HORMONES

Calcitriol

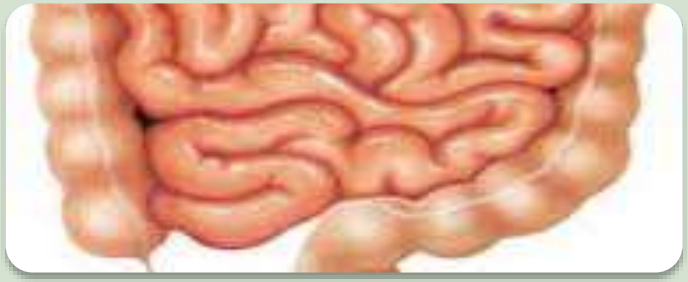
PTH

Calcitonin

REGULATION OF SERUM PHOSPHORUS

calcitriol

Increases plasma phosphorus



Increases absorption from intestine

Increases the mobilization from bone

Increases the renal reabsorption

REGULATION OF PLASMA PHOSPHORUS

PTH

Decreases plasma phosphorus

Decreases the renal reabsorption

REGULATION OF SERUM PHOSPHORUS

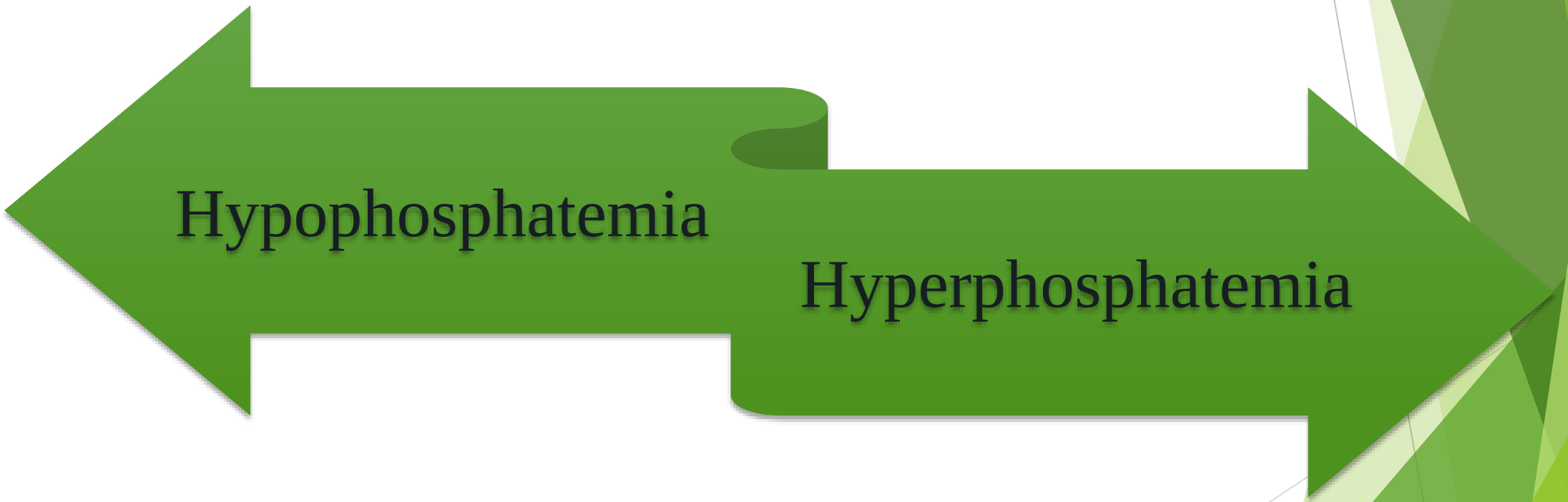
Calcitonin

Decreases plasma phosphorus

Inhibits bone resorption

Decreases the renal reabsorption

DISORDERS OF PHOSPHORUS METABOLISM



HYPOPHOSPHATEMIA

Serum inorganic phosphate concentration **<2.5 mg/dl**

Decreased intake

Decreased absorption

Increased loss

HYPOPHOSPHATEMIA - FEATURES

- Hemolytic anemia
- Leukocyte dysfunction
- Platelet dysfunction

Acute

- Anorexia
- Weakness
- Pain in the muscle and bones
- Fractures

Chronic

- In the treatment of Diabetes the effect of insulin is causing the shift of glucose into cells also enhances the transport of phosphate into cells.

- Renal rickets is associates with **low phosphate & increased ALP concentration**.

- Congenital defect of tubular phosphate reabsorption, e.g. Fanconi's syndrome, in which **phosphate is lost**.

- **Symptoms:** Hemolytic anemia, weakness, bone fractures, Muscle pain, Rickets in children & osteoporosis in adults may develop.

HYPERPHOSPHATEMIA

Serum inorganic phosphate concentration **>4.5 mg/dl**

- Increased intestinal absorption
- Decreased renal excretion
- Extracellular shift of phosphorus
- Hemolysis

FEATURES OF HYPERPHOSPHATEMIA

Chronic renal failure

Soft tissue calcification

HYPERPHOSPHATEMIA TREATMENT

Treatment of underlying disorders

Dialysis in renal failure

Administration of aluminum hydroxide


12
Mg
Magnesium
24.3050


Mg

MAGNESIUM

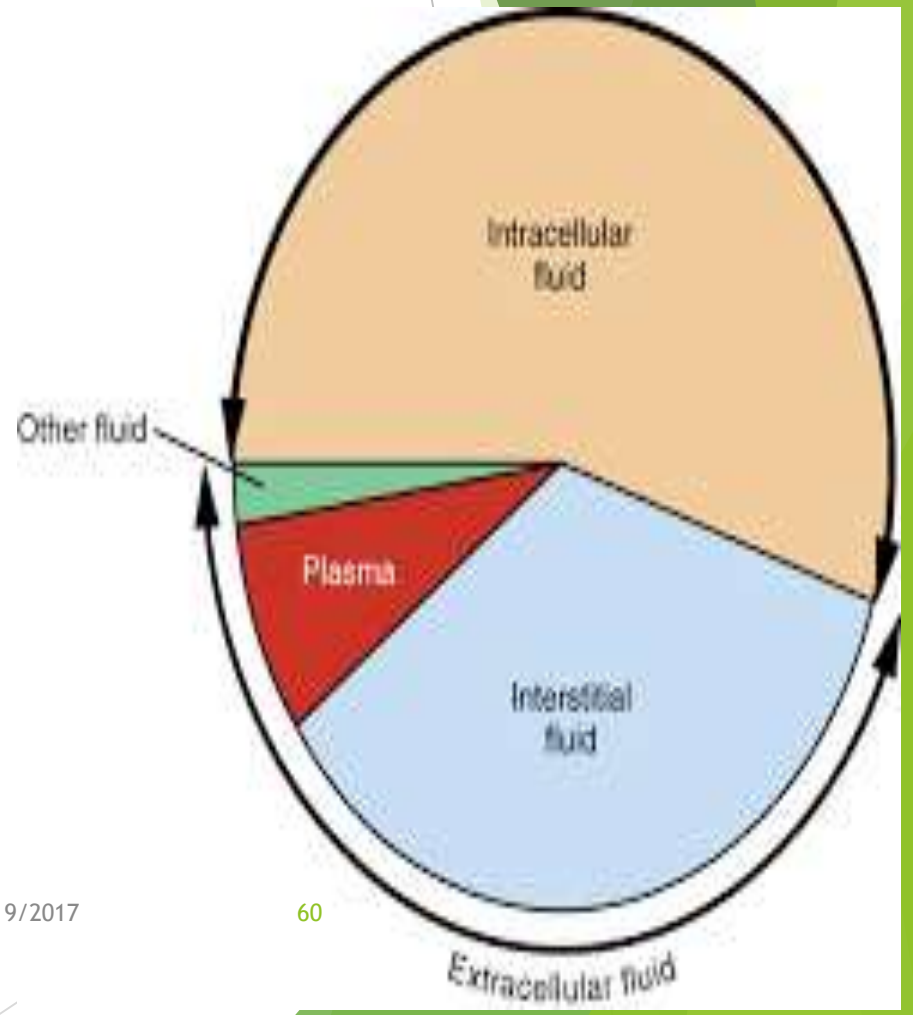
OBJECTIVES

- Distribution of magnesium
- Sources
- RDA
- Functions of magnesium
- Disorders of magnesium metabolism

INTRODUCTION TO MAGNESIUM

- Magnesium is the **fourth** most abundant cation in the body and **second** most prevalent intracellular cation.
- Human body contains – 25gm of magnesium.

- **BODY DISTRIBUTION:**
- Human body contains 25g of magnesium
- About 60% of which is complexed with calcium & phosphorous in bones
- 30% in soft tissues & 1% is in ECF



- **Sources:**

  Cereals, beans, vegetables, potatoes, meat, milk, fruits & fish

- **RDA:**
  - Adult man : 400 mg/day
  - Women : 300 mg/day
  - During pregnancy & lactation : 450 mg/day

BIOCHEMICAL FUNCTIONS

- **Magnesium is required for :**
  - ✓ Formation of bones & teeth
  - ✓ To maintain neuromuscular irritability

- **Co-factor:**

More than 300 enzymes requires magnesium as a cofactor

Hexokinase ,Glucokinase , Phosphofructokinase, Pyruvatecarboxylase, Peptidases,

Ribonucleases, Adenylate cyclase

- **Neuromuscular function:**

Necessary for neuromuscular function, low Mg+2 levels lead to neuromuscular irritability

ABSORPTION:

Small intestine & excreted in feces

Calcium, phosphate & alcohol **decreases &** PTH **increases** magnesium absorption.

- **NORMAL PLASMA LEVELS:**

Serum magnesium: **1.7 - 3 mg/dl**

70% of magnesium exists in free state

30% is protein bound (albumin)

Small amount is **complexed with anions** like phosphate & citrate.

DISORDERS

HYPOMAGNESAEMIA

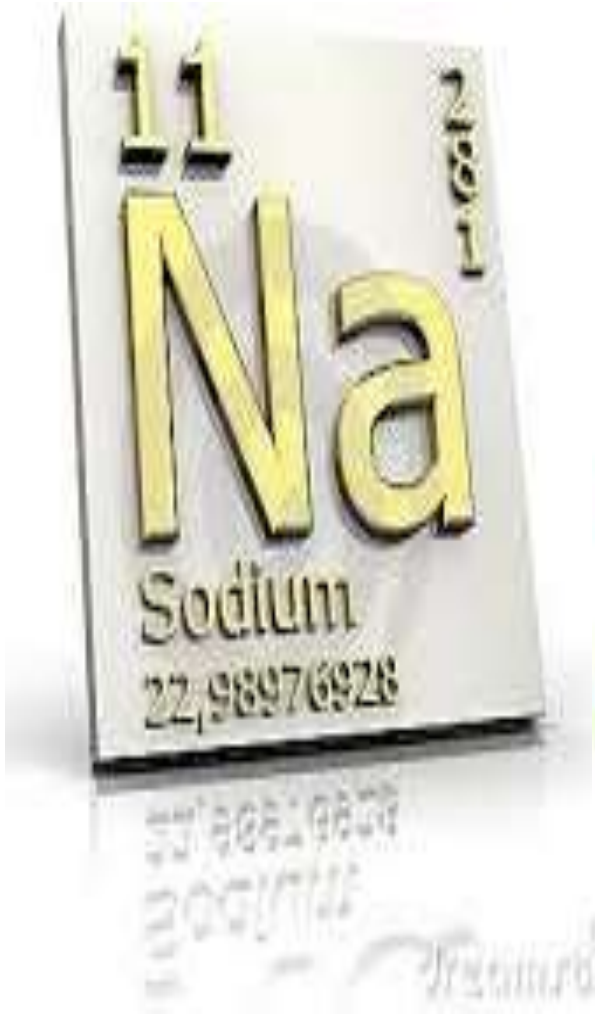
Decrease in serum magnesium levels **<1.7 mg/dl.**

- **CAUSES:**
  - Decreased intake – due to malnutrition
  - Decreased absorption – due to malabsorption
  - Increased renal loss – due to renal tubular acidosis
- **SYMPTOMS:**
  - Impaired neuromuscular function
  - Hypocalcemia – due to decreased PTH secretion
  - Tetany, Convulsions & Muscle weakness

HYPERMAGNESAEMIA

Increase in serum magnesium **> 3.5 mg/dl**

- **CAUSES:**
  - Uncommon but is occasionally seen in renal failure – decreased excretion
  - Excess intake orally or parentrally
  - Hyperparathyroidism
- **SYMPTOMS:**
  - Depression of the neuromuscular system, lethargy
  - Hypotension, bradycardia


11
Na
Sodium
22,98976928

INTRODUCTION TO SODIUM

- Sodium is the chief electrolyte. It is found in large concentration in ECF.

  - ✓ Total body content of sodium is **4000 mEq or 1.8 gm/kg**

  Approximately 50% in bones

  40% in ECF

  10% in tissues

  - ✓ Sodium is found in the body mainly associated with chlorides as NaCl

- **Sources:**
  - Table salt (NaCl), salty foods, animal foods, milk, eggs, cereals, carrot, tomato, legumes
- **RDA:**
  - 5 gm/day
- **Absorption & excretion:**
  - From GIT – Na^+ – K^+ pump
  - < 2% is normally found in feces & sweat
  - In diarrhea, large quantities of sodium is lost in feces.

BIOCHEMICAL FUNCTIONS

- Sodium is essential for
  - Maintenance of **osmotic pressure & water balance**
  - It is constituent of **buffer** & involved in maintenance of **acid-base balance**
  - It maintains muscle **irritability & cell permeability**
  - Involved in intestinal absorption of **glucose, galactose & amino acids**
  - Necessary for **initiating & maintaining heart beat**.

- **Normal serum sodium: 135-145 mEq/l**

DISORDERS OF SODIUM METABOLISM

HYPONATREMIA:

Decrease in serum sodium level **<130 mEq/l**

- **CAUSES:**

  Vomiting & Diarrhea

  Addison's disease (adrenal insufficiency)

  Real tubular acidosis (reabsorption is defective)

  Chronic renal failure & nephrotic syndrome

  Congestive cardiac failure

  Edema

SYMPTOMS OF HYPONATREMIA:

- Drop in blood pressure
- Lethergy, Confusion
- Tremors & coma

- **Hyponatremia due to water retention**:
  - Retention of water dilutes the constituents of extracellular space causing hyponatremia, e.g. heart failure, liver diseases, nephrotic syndrome, renal failure, increased ADH secretion.

TREATMENT OF HYPONATREMIA:

- ✓ Administered sodium should be closely monitored
- ✓ After sufficient time for distribution -4 to 6 hrs
- ✓ Water restriction, increased salt in take
- ✓ Anti-ADH drugs

- Sodium loss
  - ❖ Vomiting, diarrhea..
  - ❖ Urinary loses may be due to aldosterone deficiency (Addison's disease)

HYPERNATREMIA:

Increase in serum sodium concentration **> 145 mEq/l**

- **CAUSES :**

Cushing's disease **– hyper activity of adrenal cortex**

In pregnancy, steroid hormones cause sodium retention in body

In dehydration, water is predominantly lost, blood volume is decreased with increased concentration of sodium.

- **SYMPTOMS:**

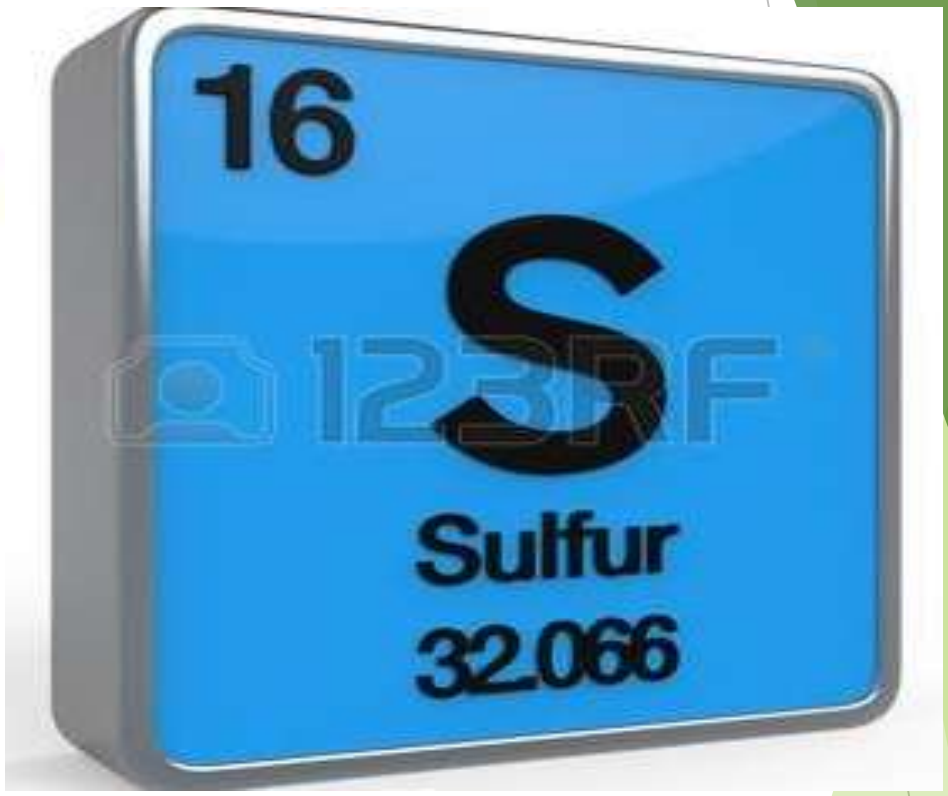
  Increase in blood volume & blood pressure

  Dry mucous membrane

  Fever

  Thirst

  Restlessness



SULFUR METABOLISM

- Sulfur is a component of several biologically important compounds.
- **Proteins** contain about **1%** sulfur by weight.
- The sulfur containing amino acids
  - **Methionine, Cysteine or Cystine**
- Sulfur containing B-complex vitamins –
  - **Thiamine (TPP), coenzyme A, lipoic acid & biotin**
- Glycosaminoglycans:
  - **Chondroitin sulfate, heparan sulfate, dermatan sulfate & keratan sulfate.**

DIETARY SOURCES

- Sulfur is present in the food as
  - **inorganic & organic sulfate** (proteins, amino acids and peptides).
- **Major sources** - proteins rich in **methionine & cysteine.**
- **ABSORPTION:**

Inorganic sulfate - from the intestine,

Organic sulfate - active transport

BIOCHEMICAL FUNCTIONS

- **Formation Of Active Sulfate (PAPS):**

- **3-Phosphoadenosine 5-phosphorsulfate(PAPS)** is active sulphate, utilized for several reactions.

  e.g. **synthesis of GAGs & detoxification**

- **Sulphur- containing amino acids** are very essential for the structural conformation & biological functions of proteins.

- **Methionine** (as S-adenosylmethionine) is actively involved in transmethylation reactions & **S-adenosylmethionine** also acts as the ***initiator*** in initiation process of protein synthesis.

- **Peptides** e.g. Glutathione & insulin

- **Iron-sulfur proteins** are found in ETC

- **Sulfur containing vitamins** (B1, B5,B7 & lipoic acid) act as coenzymes.

EXCRETION

- Sulfur is **oxidized in the liver to sulfate** and excreted.
- **Urinary sulfur** : 1 g/day
- Sulfur is excreted in urine in the form of inorganic (80%), organic or ethereal sulfate (10%) neutral sulfur or unoxidized sulfur (10%).

IODINE METABOLISM

- Total body iodine: 20 mg
- **80%** is present in the **thyroid gland.**
- Also present in muscles, salivary glands & ovaries.

BIOCHEMICAL FUNCTIONS

- Most important functions
  - Synthesis of thyroid hormones, triiodothyronine (T3) and tetraiodothyronine (T4) in thyroid gland.
  - ^{125} I is used as radioactive label in the radioimmunoassay of hormones (T3 & T4)
  - ^{131} I is used for the assessment of thyroid malignancy & treatment of thyrotoxicosis.

SOURCES:

- Sea foods, eggs, dairy products, vegetables & iodized salts.

RDA:

- **Adults:** 100 - 150 µg/day
- **Pregnant women:** 200 µg/day

METABOLISM

- From **upper small intestine.**
- Iodine is transported in plasma by loosely binding to plasma proteins.
- 80% of body's iodine is stored in the organic form as **iodothyroglobulin** in thyroid gland.
- Iodothyroglobulin contains **thyroxine, diiodotyrosine,** & **triiodothyronine**.

EXCRETION

- Iodine is excreted through urine.
- Also excreted through bile, skin & saliva.

- **Plasma iodine: 4 – 10 mg/dl.**

- Most of this is present as **protein bound iodine (PBI).**
- It represents the iodine levels.
- PBI:
  - Increased in hyperthyroidism
  - Decreased in hypothyroidism

DISEASE STATES

- **Iodine deficiency:** **GOITRE**
- **Causes:**
  - Dietary deficiency
  - Ingestion of goitrogens in the diet.
- **Dietary deficiency**:
- Low content of iodine in soil & water.
- Jammu & Kashmir, Karnataka, Punjab, Himachal Pradesh, Maharashtra & kerala show higher incidence of goiter.

GOITRE

- Abnormal increase in size of the thyroid gland is known as goitre.
  - Decreased synthesis of thyroid hormones & is associated with elevated TSH.
  - Goitre is primarily due to a failure in the auto regulation of T3 & T4 synthesis.
  - Caused by deficiency or excess of iodide

Goitrogenic Substances (Goitrogens)

- Substances that interfere with the utilization of iodine for the synthesis of thyroid hormones
- **Thiocyanates** – present in cabbage, cauliflower & they inhibit uptake of iodine by thyroid glands.
- Drugs - thiourea, thiouracil, thiocarbamide – inhibits iodination process.

Simple Endemic Goitre

- **Iodine deficiency** is known as simple goitre.
- Characterized by **swelling of thyroid gland & features of hypothyroidism.**
- Iodine deficiency in **pregnant women results in impaired fetal growth & brain development.**
- **TREATMENT:**
- Consumption of iodized salt is advocated
- Administration of thyroid hormone is also employed.

MANGANESE METABOLISM

- Total body content of manganese is **15 mg**
- Present in the **liver & kidney**.
- It is associated with connective & bony tissue, growth & reproductive functions, carbohydrate & lipid metabolism.
- **Sources:**
  - Liver, kidneys, whole grain cereals, vegetables & nuts.
  - Tea is a rich source of manganese.

- **RDA:**
  - 2.5 to 5 mg/day.
- **Serum manganese**: 5-20 mg/dl.
- **Absorption**: From the small intestine.
- Calcium, phosphorous & iron inhibit manganese absorption.

Biochemical functions

- **Role in enzyme action:**
- Acts as a ‘cofactor’ or activator of many enzymes like
  - **Arginase,**
  - **Isocitrate dehydrogenase (ICD),**
  - **Cholinesterase,**
  - **Lipoprotein lipase,**
  - **Enolase,**
  - **Pyruvate carboxylase**
  - **SOD (Mitochondria)**

- Manganese is essential for
  - Formation of bone, proper reproduction, functioning of nervous system
  - Hemoglobin synthesis
  - Inhibition of lipid peroxidation
  - Cholesterol & fatty acid biosynthesis
  - Function with vitamin K in the formation of prothrombin.

Deficiency & toxicity

- Manganese deficiency is not seen in humans, adequate supply in normal diet
- **Manganese deficiency** in animals causes:
  - Retarded growth, bone deformities, sterility.
  - Fatty liver, increased ALP, diminished activity of β –cells of pancreas.
- **Toxicity:**

  Caused by industrial exposure to manganese.
- **Symptoms**: Psychiatric

Fluorine Metabolism

Fluorine

- It is mainly found in bones & teeth.
- The content of fluorine in water is dependent on the soil content of fluorine.
- **RDA:** 1-2 p/m (parts per million).
- Fluorine is supplemented in various tooth paste preparations.

- **Fluorinated toothpaste** contains **3,000 ppm** of fluoride.

- Even **ordinary toothpaste** contains fluoride about **700 ppm.**

- **Normal blood level** - 4 microgram/100 ml.

Biochemical functions

- Required for the proper **formation of bones & teeth.**
- Fluoride, **prevents the development of dental caries.**
- It forms a protective layer of **acid resistant fluoroapatite with hydroxyapatite of enamel**, which increases hardness of bone & teeth & provides **protection against dental caries** & attack by acids.
- **Sodium fluoride** inhibits **enolase** & **fluoroacetate** inhibits **aconitase.**

Absorption and excretion

- **Inorganic fluoride** is absorbed readily in the **stomach & small intestine** and distributed almost entirely to bone and teeth.

- About 50% of the daily intake is **excreted through urine.**

Deficiency & toxicity

- **Causes:**

  Drinking water that is low in fluorine content.

  Fluorine deficiency causes dental caries.

- **Toxicity:**

  Drinking water contains >5 ppm of fluorine.

- **Features:**

  Result in **dental fluorosis** & **skeletal fluorosis.**

- ***DENTAL FLUOROSIS:***

  It is an important public health problem in several countries including India.

- **Features:**

  It is characterized by mottling of enamel & discoloration of teeth.

- ***SKELETAL FLUOROSIS:***

  If the ingestion of fluorine is very high (more than 10 ppm), the condition leads to skeletal fluorosis

- **Features:**
- ***Hypercalcification*****,** increasing the density of bones of limbs, pelvis & spine.
  - Bone deformities such as bowed legs, bending of spine & osteoporosis.
  - Ligaments of spine & collagen of bones also calcified.
- In advanced stages,
  - Individuals cannot perform their routine work due to stiff joints.
  - Advances fluorosis is referred to as **genu valgum** .

Selenium Metabolism

Selenium

- Total body content of selenium 10 mg
- Mainly present in liver.
- Selenium was found to prevent liver cell necrosis & muscular dystrophy.
- **Sources:**
  - Meat, sea foods, liver, kidney
- **RDA:** 50 to 100 µg/day.
- **Normal serum level** is 50-100 microgram/dl.

Absorption and excretion

- **Absorption** starts from the **duodenum**.
- After absorption, transported by plasma proteins particularly β-lipoproteins
- **Excreted** through **urine.**

BIOCHEMICAL FUNCTIONS

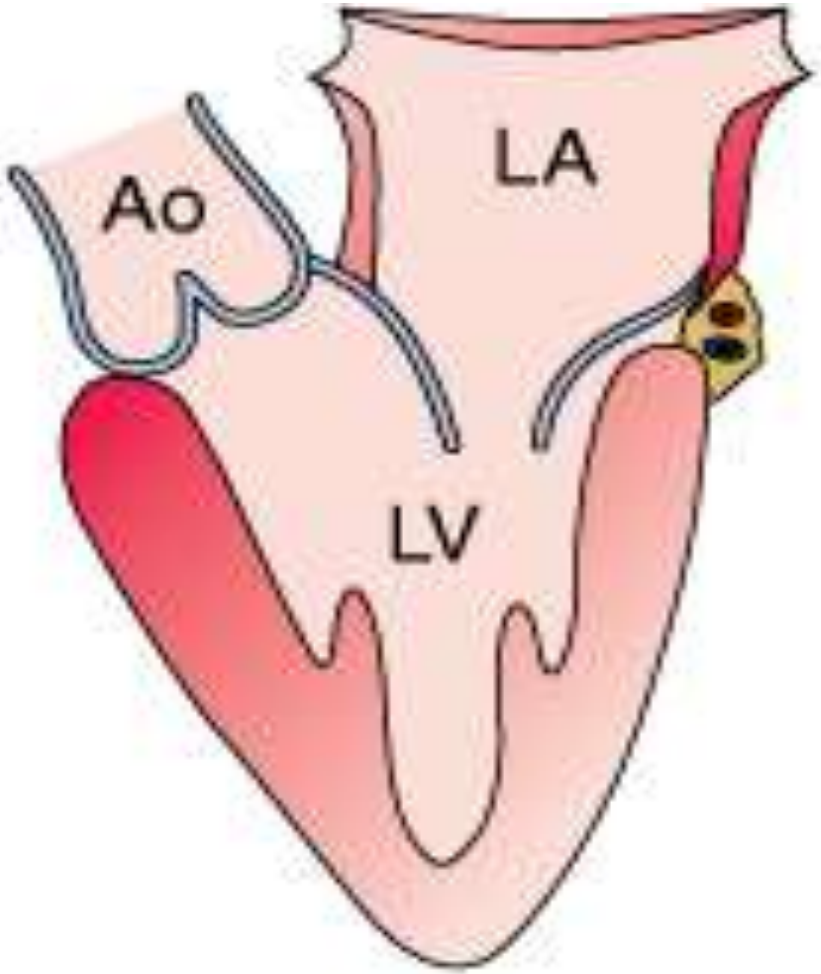
- Selenium
  - Along with vitamin E, prevents development of hepatic necrosis & muscular dystrophy
  - Involved in maintaining structural integrity of cell membranes.
  - **Selenocysteine** is an essential component of glutathione peroxidase (antioxidant enzyme)
  - Prevents lipid peroxidation & protects the cells against free radicals.

- Binds with certain heavy metals (Hg, Cd) & protects the body from their toxic effects.
- **5'-deiodinase-** selenium containing enzyme converts thyroxine (T4) to triiodithyronine (T3) in thyroid gland.
- In **selenium deficiency**, conversion of **T4 to T3** is impaired resulting in **hypothyroidism**.
- **Thioredoxin reductase** – contains selenium, involved in purine metabolism.

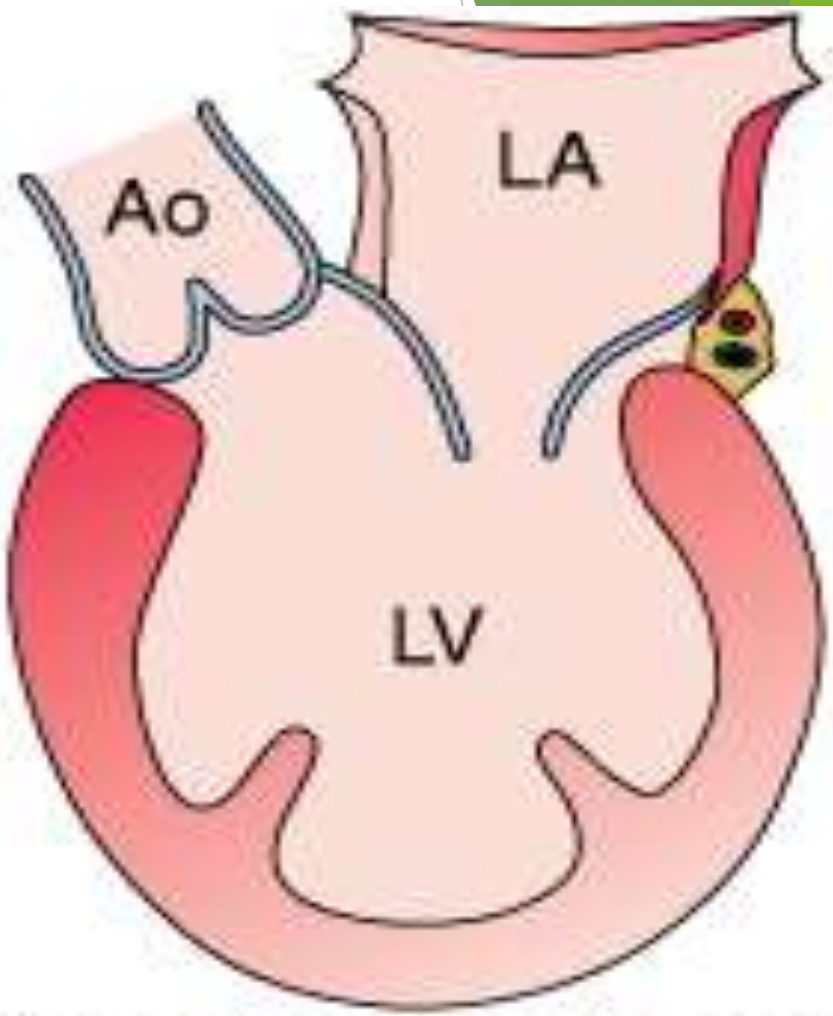
- Selenium in the diet reduces the requirement of vitamin E.
- Selenium may exert anticancer effects because of its antioxidant role.
- ***Selenocysteine*** is considered as **21st amino acid**, it is coded by UGA, which is a termination codon.
- Selenium is incorporated to proteins as selenocysteine during protein synthesis.

Deficiency

- **Causes:**
  - Low soil content of selenium & malnutrition.
- **Clinical features:**
- **Keshan disease, an endemic cardiomyopathy in China**
  - Associated with cirrhosis of liver
  - Cardiomyopathy leading to congestive cardiac failure,
  - Multifocal myocardial necrosis
  - Cardiac arrythmias



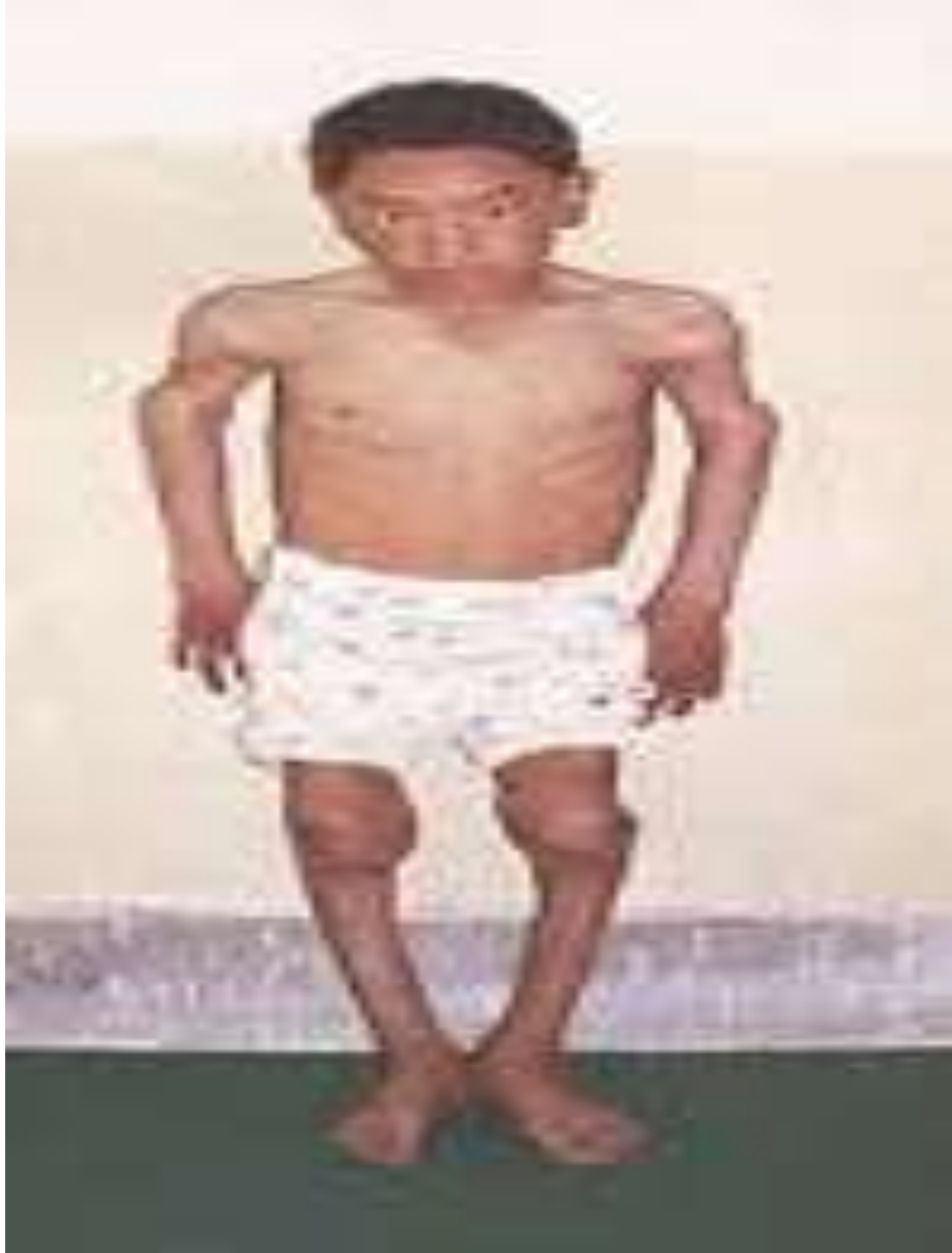
Normal



Dilated cardiomyopathy

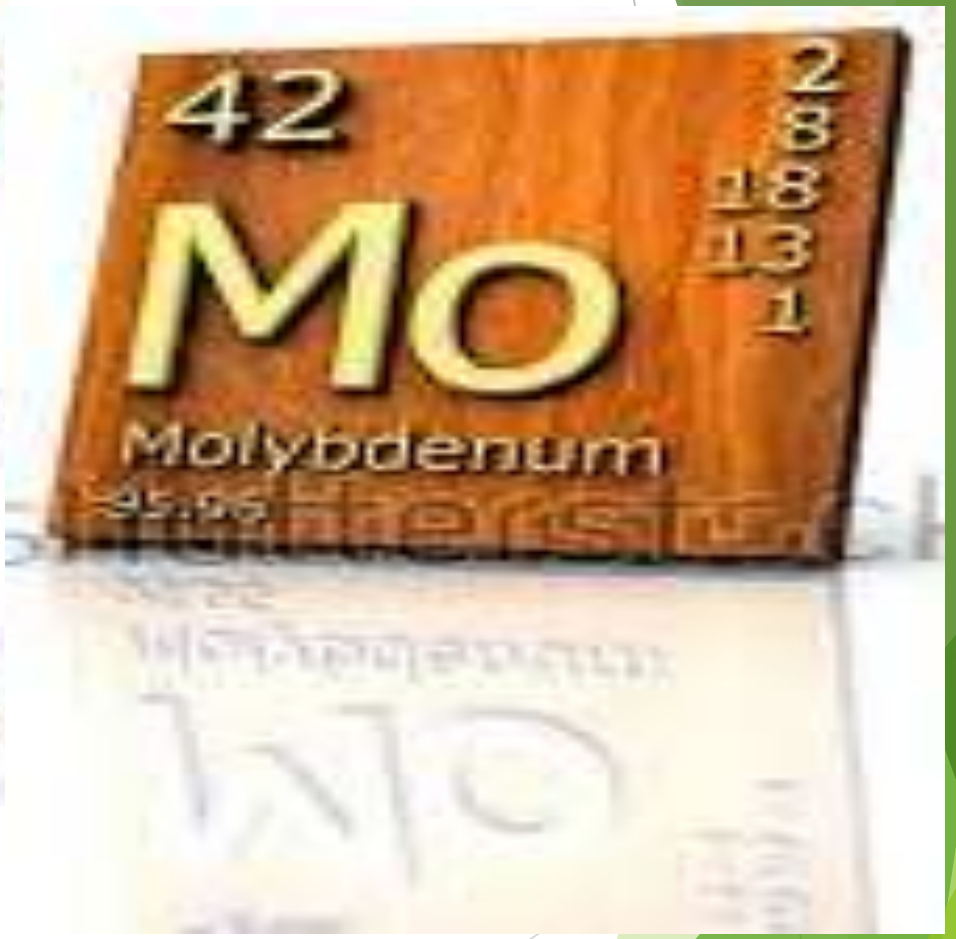
Keshan Disease

- Muscular dystrophy
- Loss of appetite
- Nausea



Selenium toxicity

- Selenium toxicityis very rare and is called as **Selenosis**
- Seen in people who handle metal polishes & anti-rust compounds.
- Clinical features
  - Hair loss
  - Dermatitis & irritability
  - Diarrhea & weight loss



MOLYBDENUM METABOLISM

MOLYBDENUM

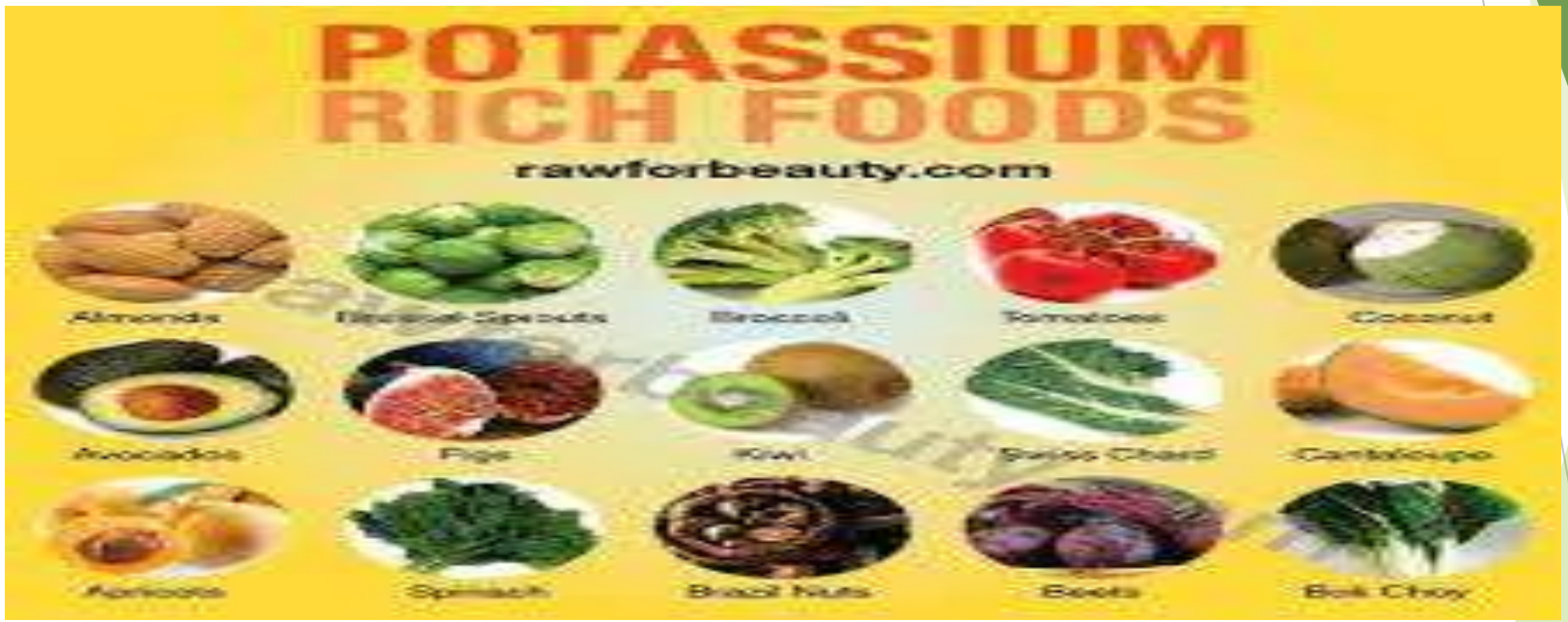
- It is a constituent of the enzymes xanthine oxidase, aldehyde oxidase, sulfite oxidase.
- **Sources:** milk, beans, cereals.
- **RDA**: 200 μg/day
- **Absorbed** by small intestine.
- **Deficiency:** Very rare in humans.
- **Toxicity**: Seen in areas where the molybdenum content of soil is very high.
- **Feature**: Growth failure, anemia, diarrhea & gout.

POTASSIUM METABOLISM

- Potassium is the major **intracellular cation**.
- About **98%** of potassium is in **cells**, only **2%** is in **ECF.**
- Total body potassium in an **adult male** is about **50 mEq/kg** of body weight as most of the body's potassium is found in muscles.

SOURCES

- Vegetables, fruits, whole grains, meat, milk, legumes and tender coconut water



RDA:

- 2 to 5 gm/day.

ABSORPTION & EXCRETION

- Potassium is readily absorbed by **passive diffusion** from GIT.
- The amount of potassium in the body depends on the balance between potassium intake and output.
- Under the normal conditions loss of potassium through gastrointestinal tract and skin is very small.
- The major means of potassium **excretion** is by the **kidney.**
- Potassium output occurs through three primary routes;**the GIT, the skin & the urine**.

FUNCTIONS

- The **depolarization & contraction of heart** require potassium.
- During **transmission of nerve impulses**, there is **sodium influx** and **potassium efflux**; with depolarization.
- **After** the nerve transmission, these **changes are reversed**.
- The **intracellular concentration gradient** is maintained by the **Na+-K+ ATPase pump.**
- The relative concentration of intracellular to extracellular potassium determines the **cellular membrane potential.**

- Potassium influences **the muscular activity.**
- Certain enzymes such as pyruvate kinase require K^+ as cofactor.
- Involved in neuromuscular irritability and nerve conduction process.
- Potassium is required for proper biosynthesis of proteins by ribosomes.
- **Normal serum potassium concentration:** 3.5 to 5 mEq/L.

DISORDERS OF POTASSIUM METABOLISM

HYPOKALEMIA (below 3 mmol/L.)

- **Hypokalemia** is clinical condition associated with **low plasma potassium concentration.**
- **CAUSES:**

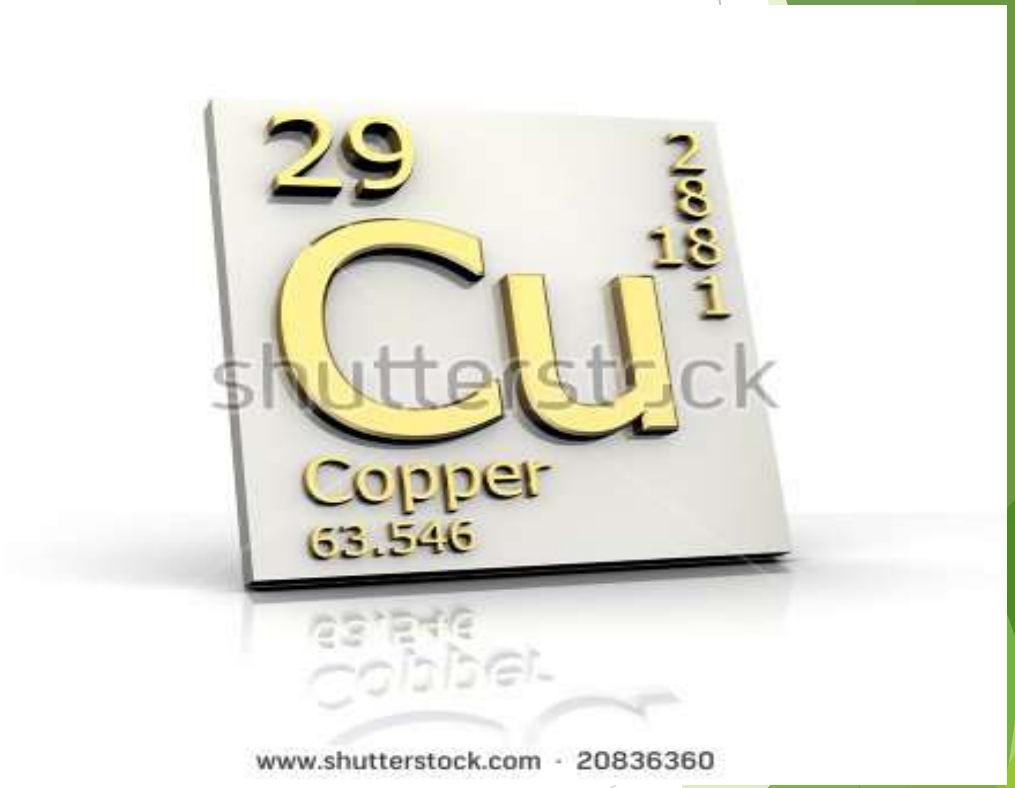
1. INCREASED RENAL EXCRETION ✓**Cushing's syndrome** ✓**Hyperaldosteronism** ✓**Hyper reninism, renal artery stenosis** ✓**Hypomagnesemia** ✓**Renal tubular acidosis** ✓**Adrenogenital syndrome**	**2. SHIFT OR REDISTRIBUTION OF POTASSIUM** ✓**Alkalosis** ✓**Insulin therapy** ✓**Thyrotoxic periodic paralysis (abnormal Na-K-ATPase)** ✓**Hypokalemic periodic paralysis (abnormal calcium channels)**
3. GASTROINTESTINAL LOSS ✓Diarrhea, vomiting, aspiration ✓Deficient intake or low potassium diet ✓Malabsorption ✓Pyloric obstruction	**4. IV SALINE INFUSION IN EXCESS** **5. DRUGS** ✓Insulin ✓Salbutamide ✓Osmotic diuretics ✓Corticosteroids

HYPERKALEMIA (above 5.5 mmol/L)

- **Hyperkalemia** is a clinical condition associated with **elevated plasma potassium** above the normal range.
- **CAUSES:**

1. <u>DECREASED RENAL EXCRETION OF POTASSIUM</u> **✓Obstruction Of Urinary Tract** **✓Renal Failure** **✓Deficient Aldosterone *(ADDISON'S)*** **✓Severe Volume Depletion *(HEART FAILURE)***	**2. <u>PSEUDOHYPERKALEMIA</u>** **✓Factitious (K+ leaches out when blood is kept for a long time before separation)** **✓Improper blood collection *(HEMOLYSIS)*** **✓Thrombocytosis *(>400 million/ml)*** **✓Leukocytosis *(>11 million/ml)***
3. <u>REDISTRIBUTION OF POTASSIUM TO EXTRACELLULAR</u> ✓Metabolic acidosis ✓Insulin deficiency (diabetes mellitus) ✓Tissue hypoxia	**4. <u>HYPERKALEMIC PERIODIC PARALYSIS</u>** **5. <u>DRUGS</u>** ✓Spiranolactone ✓Beta blockers ✓Cyclosporine ✓Digoxin

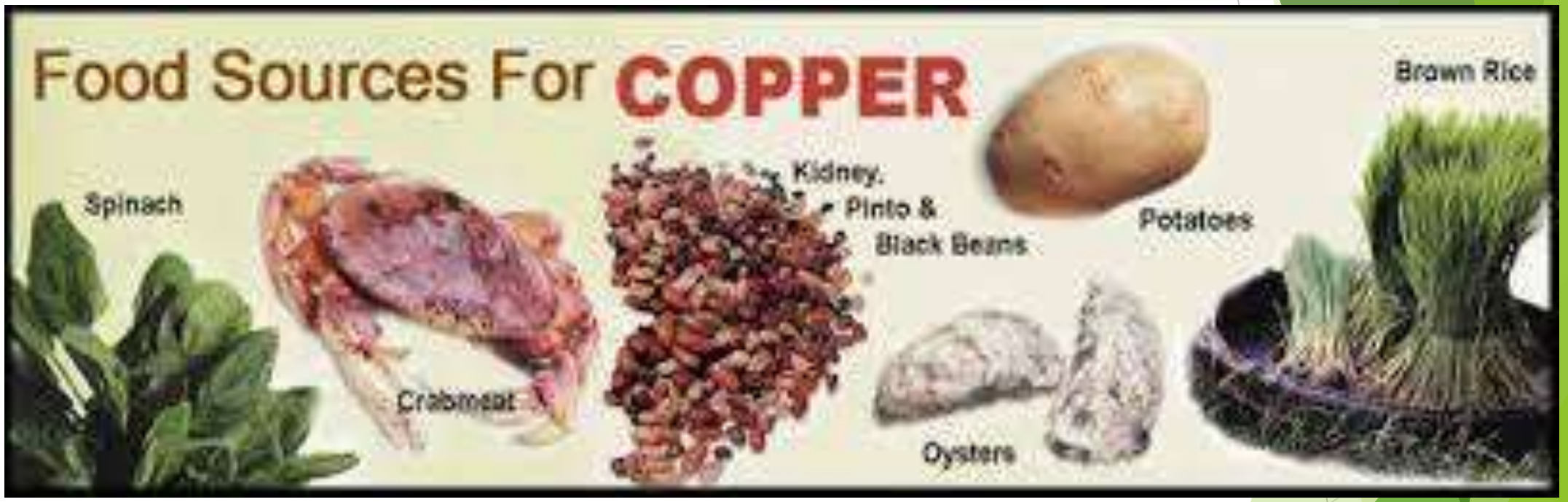
COPPER METABOLISM



- Total body copper is about **100 mg.**
- It is present in all tissues.
- The highest concentrations are found in **liver, kidney**, with significant amount in **cardiac and skeletal muscle & in bone.**
- Excess of copper is **excreted in bile** and then into **gut.**

SOURCES:

- Shellfish, liver, kidneys, egg yolk & some legumes are rich in copper.



- **RDA:**

2 to 3 mg/day.

BIOCHEMICAL FUNCTIONS

- Copper is an essential constituent of **several enzymes**.
- These include **cytochrome oxidase, catalase, tyrosinase, superoxide dismutase, monoamine oxidase, ascorbic acid oxidase, ALA synthase, phenol oxidase and uricase.**
- Copper is involved in many **metabolic reactions**.
- Copper is necessary for the **synthesis of haemoglobin.**
- **Lysyl oxidase** (a copper-containing enzyme) is required for the conversion of certain **lysine residues of collagen & elastin to allysine.**

- **Ceruloplasmin** serves as **ferroxidase** & is involved in the conversion of iron from Fe^{2+} to Fe^{3+}
- Copper is necessary for the synthesis of **melanin & phospholipids.**
- Development of **bone & nervous system** (myelin) requires Cu.
- These include **hepatocuprein** , **cerebrocuprein** and **hemocuprein**.
- **Hemocyanin,** a copper **protein complex** in invertebrates, functions like **hemoglobin for O_2 transport.**

METABOLISM OF COPPER

Absorbed from **upper small intestine.**

- Absorbed copper is transported to the **liver bound to albumin** & **exported to peripheral tissues** mainly as **ceruloplasmin** & to **lesser extent to albumin**.

- **Metallothionein** is a **transport protein** that facilitates **copper absorption**.

- **Phytate, zinc & molybdenum** decrease copper uptake.

- **Plasma copper:** ***100 – 200 mg/dl.***

- Most of this (95%) is **tightly bound to ceruloplasmin**, small fraction is **loosely held to albumin**.

- **Plasma ceruloplasmin**: ***25 – 50 mg/dl.***

DEFICIENCY

Copper deficiency is caused by malnutrition, malabsorption & nephrotic syndrome .

- **Clinical Features:**
- Neutropaenia (decreased number of neutrophils)
- Hypochromic anemia in the early stages.
- Osteoporosis & bone & joint abnormalities, due to impairment in copper-dependent cross-linking of bone collagen and connective tissue
- Decreased pigmentation of skin due to depressed copper dependent tyrosine kinase activity.
- Neurological abnormalities probably caused by depressed cytochrome oxidase activity.

Menkes Syndrome Or Kinky-hair Disease

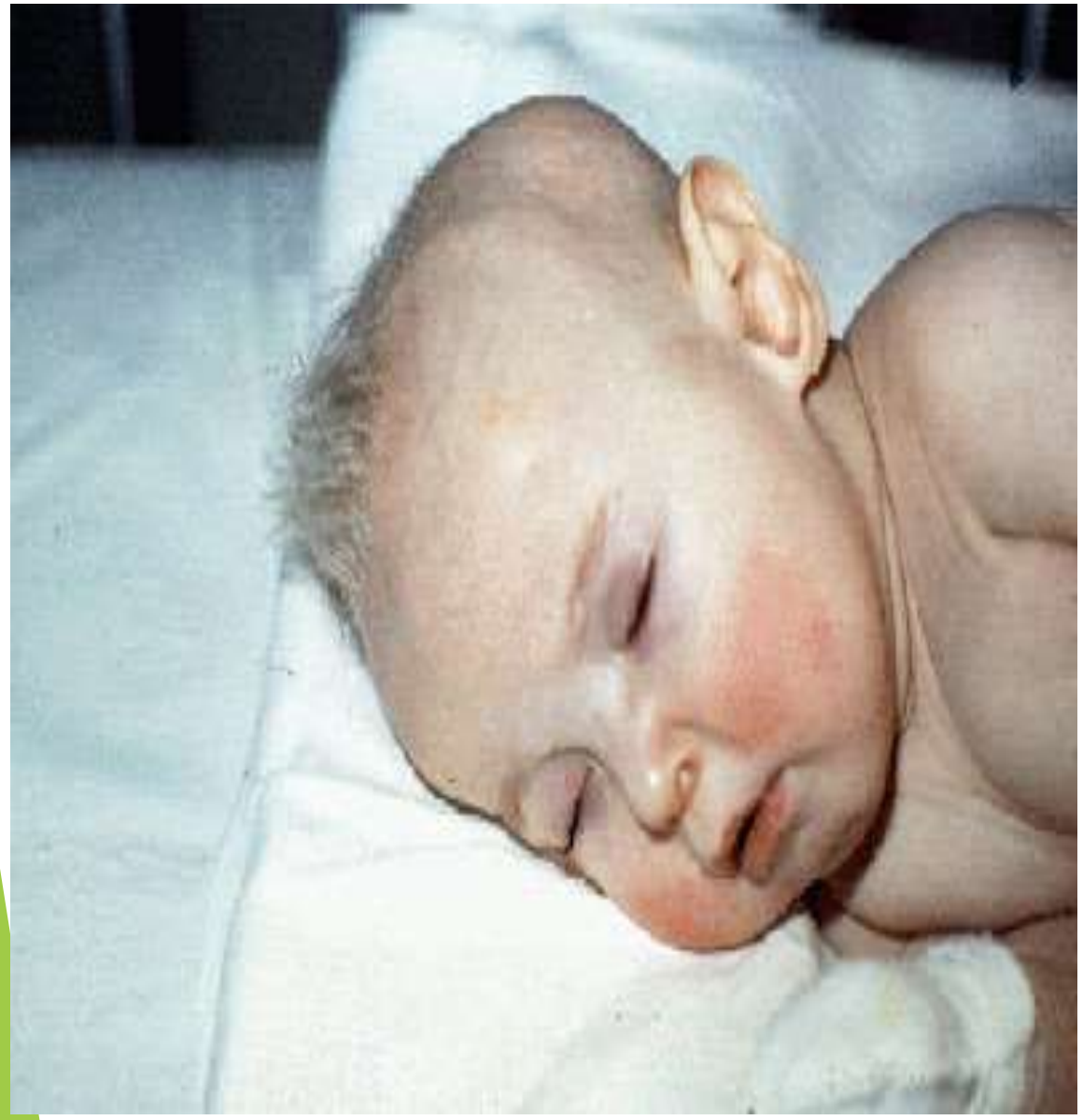
- It is a **rare disorder** & inherited as **sex linked recessive** disorder.
- Caused by **mutation in the gene** that codes for **copper binding P type ATPase** in the intestinal mucosal cell to **defect in the transport** of copper from **intestinal mucosal cell to blood.**
- This leads to **decreased intestinal absorption** of copper.
- It is possible that copper may be trapped by **metallothionein in the intestinal cells**.

- **Symptoms:**

Includes:-

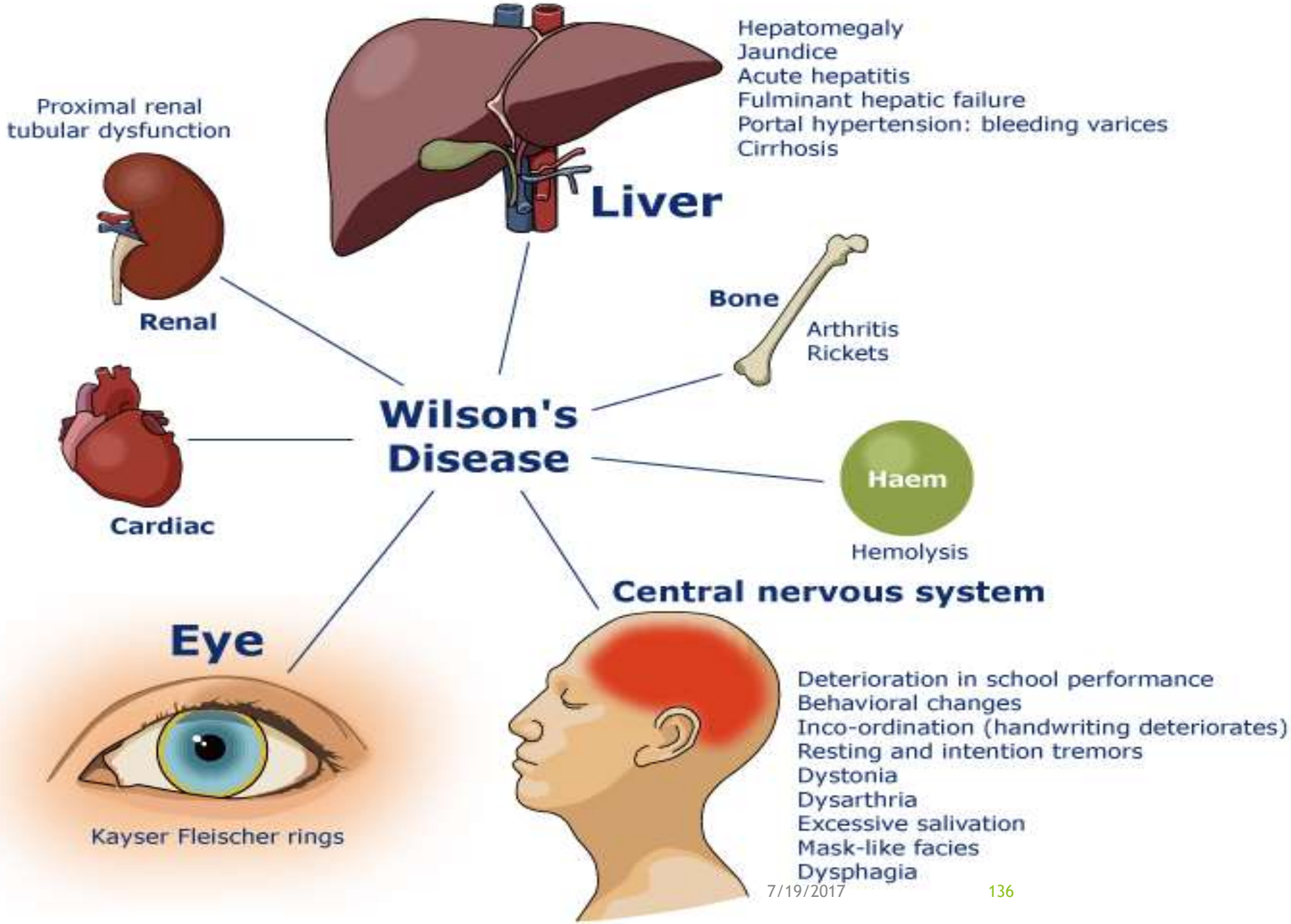
I. Decreased copper in plasma and urine
II. Anemia,
III. Depigmentation of hair,
IV. Growth failure,
V. Mental retardation,
VI. Vascular defects (lesions of the blood vessels).

MENKES SYNDROME



Wilson’s disease

- Wilson’s disease (***hepatolenticular degeneration***) is a **rare genetic disorder**.
- **Autosomal recessively** inherited disorder.
- Wilson’s Disease gene **ATP7B** encodes a copper transporting **P-Type ATPase** which is expressed predominantly in liver
- Leading to defect in the **transport of copper & secretion of ceruloplasmin from the liver.**
- This results in **accumulation of copper in the liver** and subsequently other tissues of the body.
- Disease is a **fatal and death occurs** at early life.


Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Portal hypertension: bleeding varices
Cirrhosis
Liver
Proximal renal tubular dysfunction
Renal
Bone
Arthritis
Rickets
Wilson's Disease
Cardiac
Haem
Hemolysis
Central nervous system
Eye
Kayser Fleischer rings
Deterioration in school performance
Behavioral changes
Inco-ordination (handwriting deteriorates)
Resting and intention tremors
Dystonia
Dysarthria
Excessive salivation
Mask-like facies
Dysphagia

Characteristics of wilson’s disease

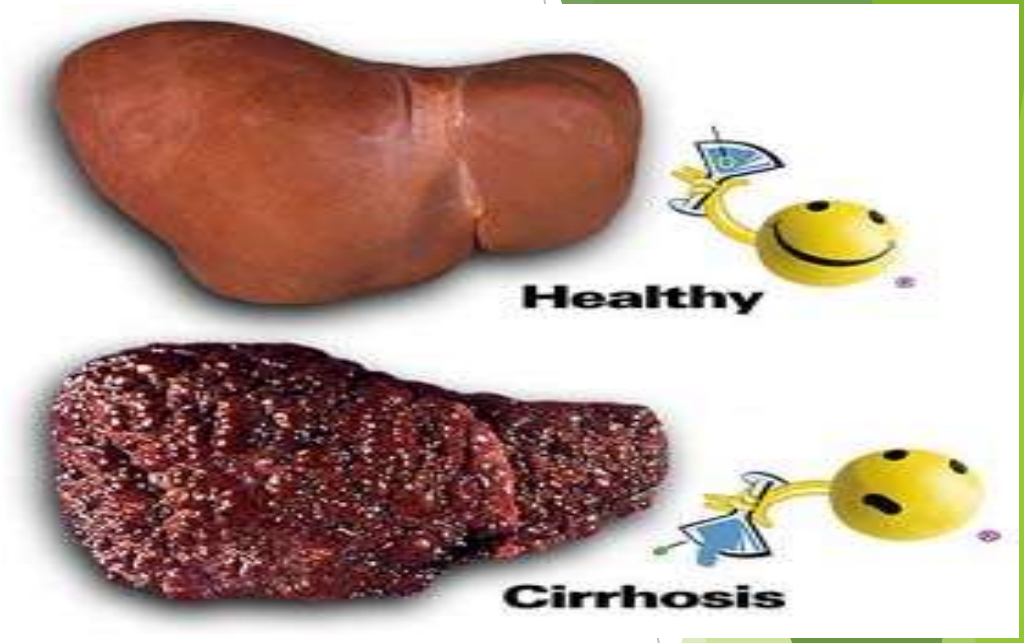
- Copper is deposited in **abnormal amounts in liver** and **lenticular nucleus** of brain.
- This may lead to **hepatic cirrhosis & brain necrosis**.
- **Low levels** of copper and ceruloplasmin in plasma with **increased excretion** of copper in **urine.**
- Copper deposition in **kidney causes renal damage.**
- This leads to **increased excretion of amino acids, glucose, peptides & hemoglobin in urine.**
- **Intestinal absorption** of copper is **very high,** about 4-6 times higher than normal.

Causes Of Wilson's Disease

- A failure to **synthesize ceruloplasmin** or an **impairment in the binding capacity** of copper to this protein or both.
- Copper is **free in the plasma**, it easily enters the tissues (**liver, brain, kidney),** binds with the proteins & gets deposited.
- **Albumin bound copper** is either normal or increased
- Copper **accumulates** particularly in **liver, brain, kidney and eyes** leading to copper toxicosis.
- Causes **neurological symptoms**, **liver damage leading to cirrhosis**, **renal tubular damage** and **Kayser-Fleisher rings** (brown pigment around the iris) at the edges of the cornea due to deposition of copper in the cornea.

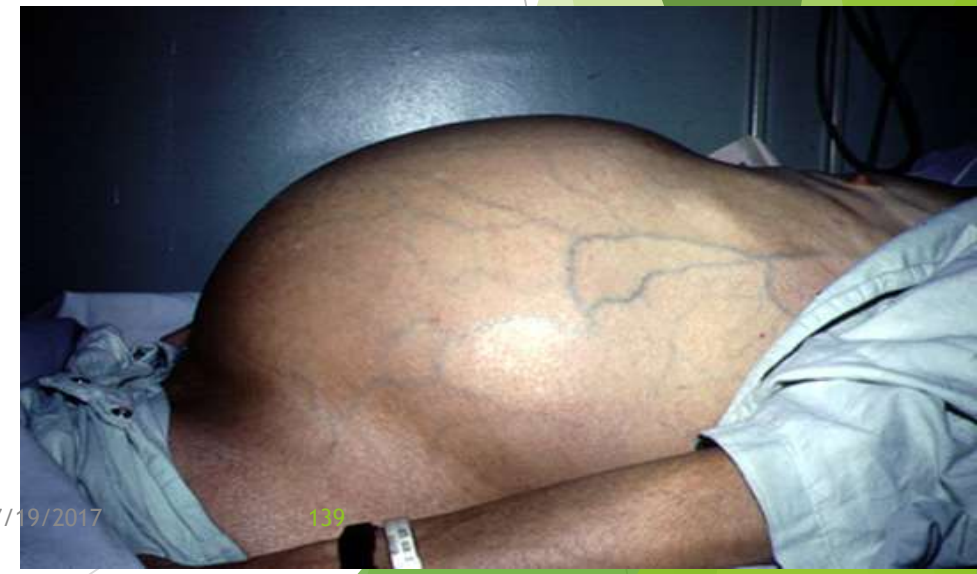
SIGNS & SYMPTOMS

- Patients present with hepatitis , cirrhosis
- WD may manifest as severe hepatic failure

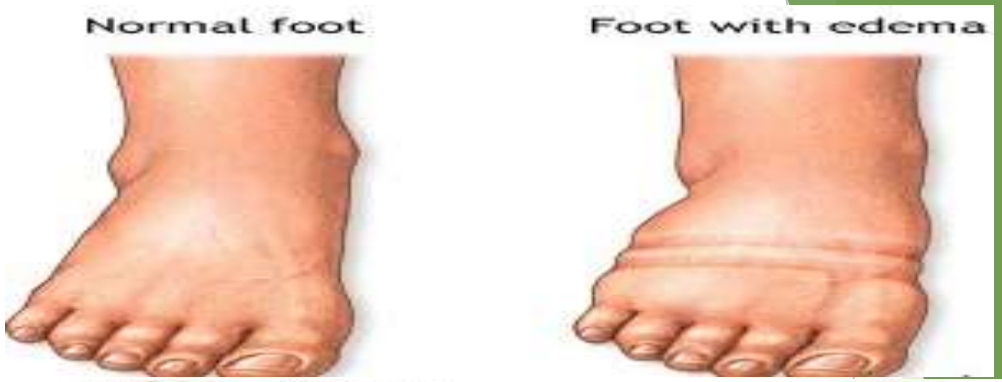


- Hepatic decompensation associated with :

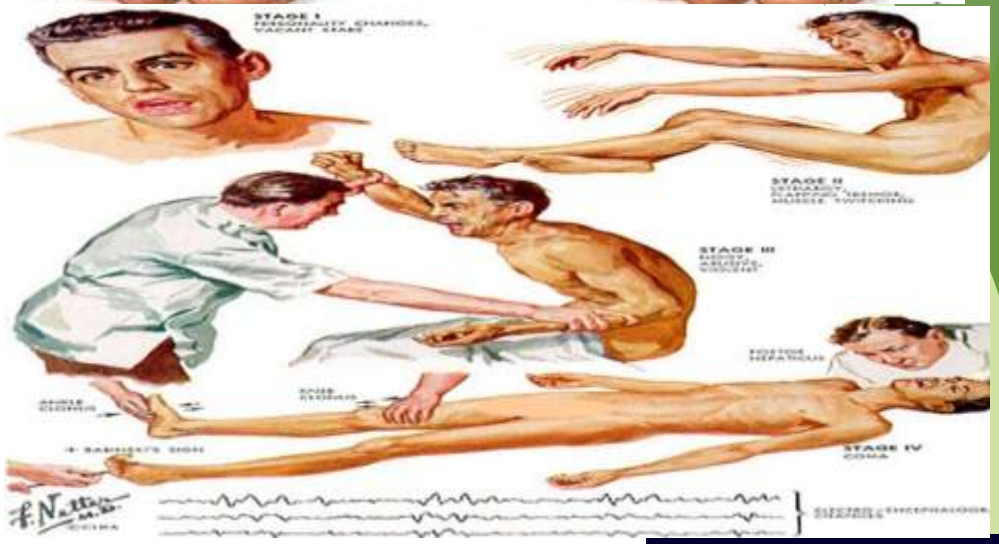
ASCITES



- Peripheral Oedema



- Hepatic Encephalopathy



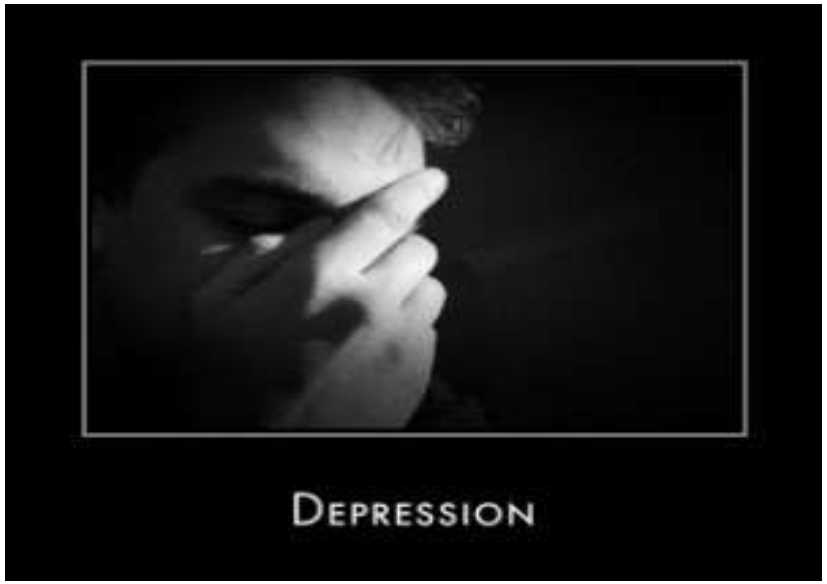
- Neurological Presentation:

DYSTONIA

TREMOR

INCOORDINATION

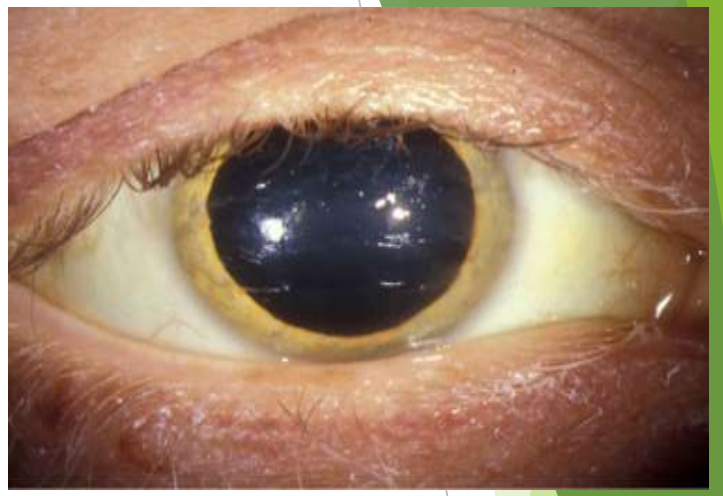
- PSYCHIATRIC PRESENTATON
  - Loss of emotional control
  - Aggressive & Anti-social behaviours
  - Depression



OCCULAR SIGNS

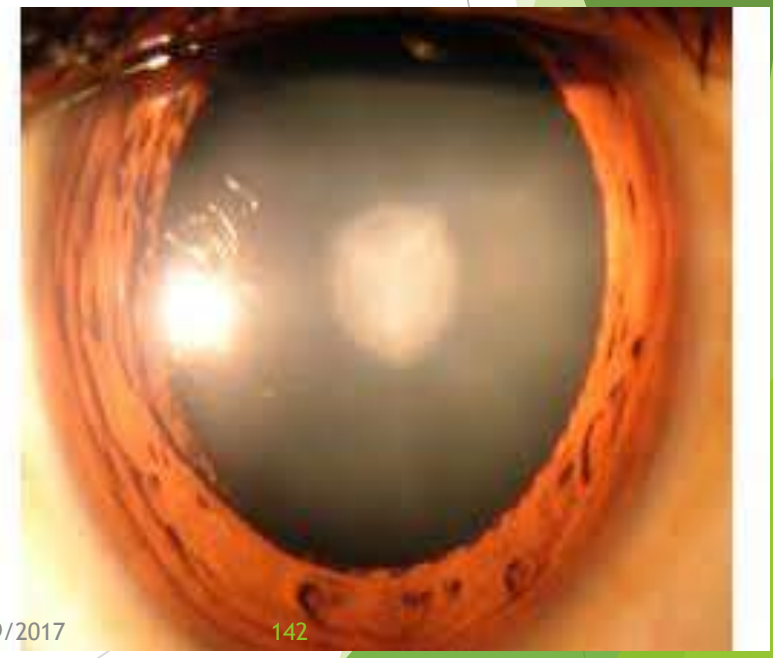
- ***KAYSER FLEISHER RING***

caused by Cu deposition in Descemet's membrane
Of cornea.



- ***SUNFLOWER CATARACTS***

due to Cu deposition in the lens.



LABORATORY DIAGNOSIS

- Presence of **KAYSER FLEISHER RING**

- **Caeruloplasmin leve**l < 20mg/day

- **Urinary copper excretion rate** > 100mg/day
- **Hepatic copper concentration :**

  Liver Biopsy with sufficient tissue reveals levels of > 250mg/g of dry weight.
- **Imaging studies:**

  CT & MRI of brain and abdomen can be carried out to confirm diagnosis

TREATMENT

- **D-PENICILLAMINE(previously used because toxic)**

➢***Mode*** : general chelator

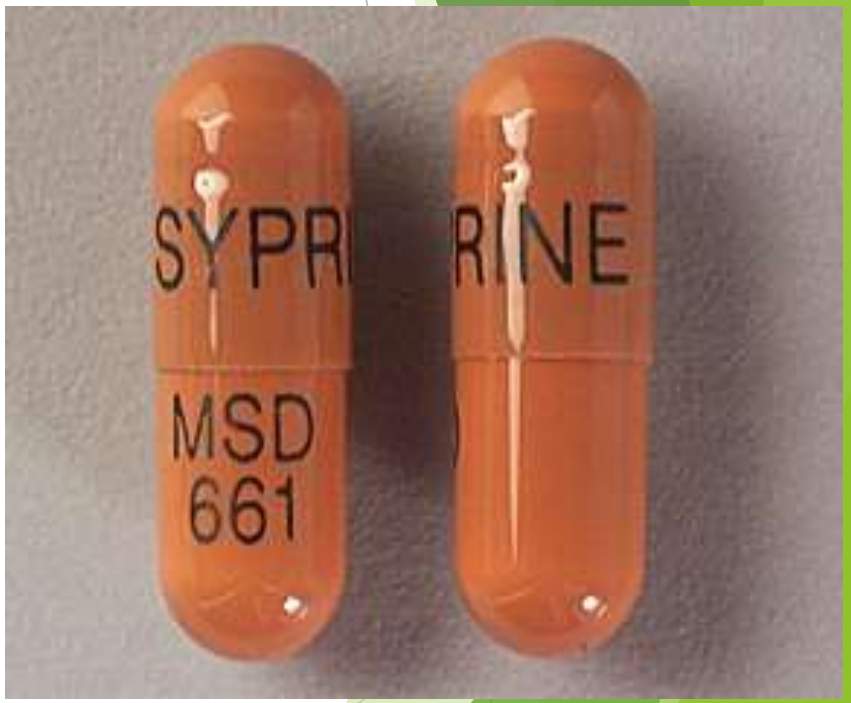
: induces urinary Cu excretion

➢***Dose Initial*** : 1-1.5g/day for adults

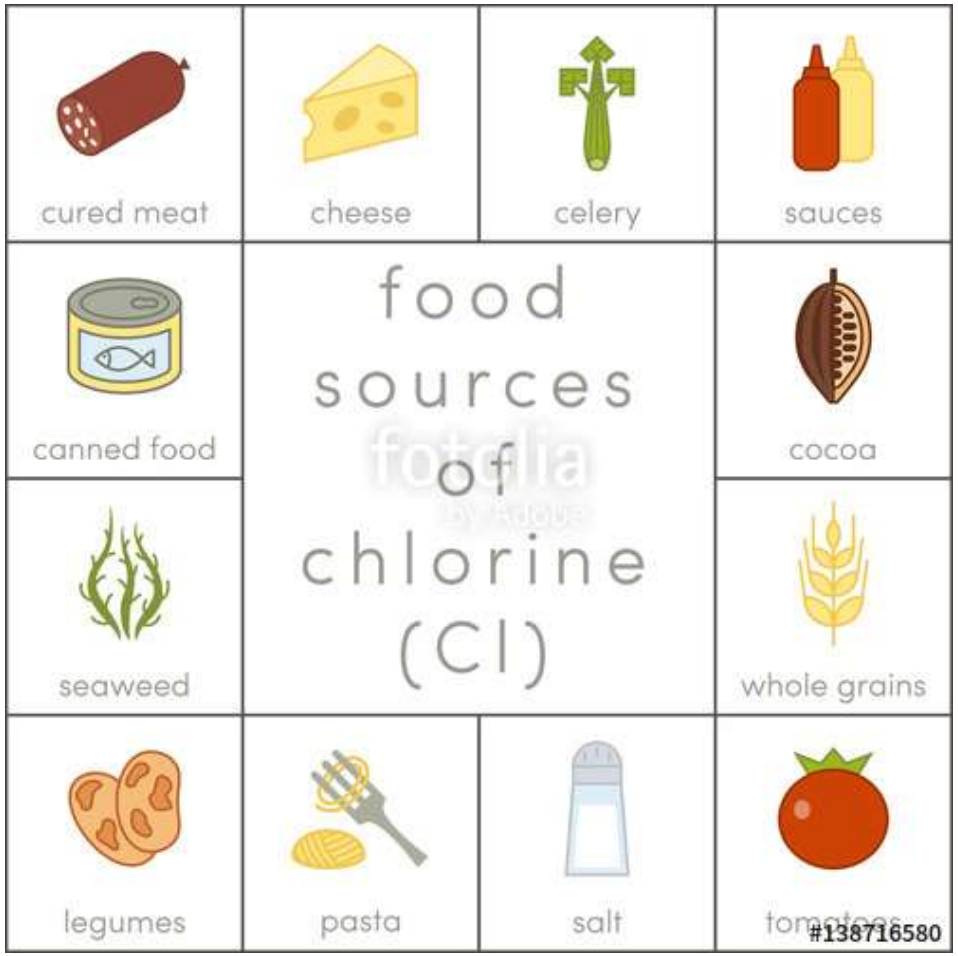
: 20mg/kg/day for children

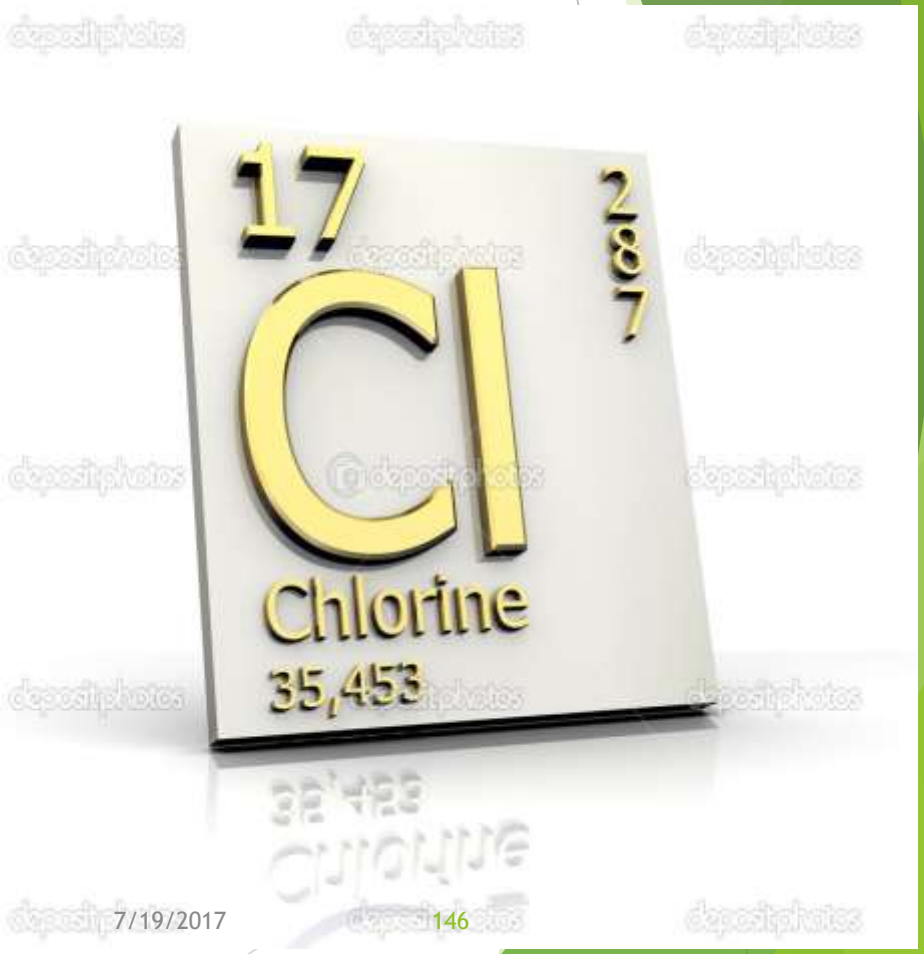
➢ ***Side Effects*** : fever, rash, aplastic anaemia leukopenia,nephrotic syndrome, thrombocytopenia

- **TRIENTINE**
  - Less toxic
  - ***Mode*** : general chelator
    : induces urinary copper excretion
  - ***Dose*** : 1-1.2g/day
  - ***Side effects*** : gastritis, aplastic anaemia



CHLORINE METABOLISM





CHLORINE

- Chlorine is the **major anion in the ECF**
- In the normal adult body, chloride is about **30mEq/kg** of body weight.
- Approximately, **88%** of the chloride is found **in the ECF**, **12% in the ICF.**

- **Sources:**
- Table salt, leafy vegetables, eggs, milk.

- **RDA: 2 to 5 gm/day.**

FUNCTIONS

- In sodium chloride, **chloride** is essential **for water balance**, **regulation of osmotic pressure** and **acid-base balance**.

- Chloride is necessary for the **formation of HCL** by the gastric mucosa and for the **activation of enzyme amylase**.

- It is involved in **the chloride shift**.

ABSORPTION AND EXCRETION

- Rapidly and almost totally **absorbed in the gastrointestinal tract.**
- Under normal conditions **chloride excretion** occurs in three ways; the **GIT, the skin & urinary tract.**
- **Chloride is excreted**, mostly as **sodium chloride** & chiefly by way of the **kidney.**
- About 2% is eliminated through the faeces.
- **Plasma chloride: 95 to 105 mEq/L**

DISORDERS OF CHLORIDE METABOLISM

HYPOCHLOREMIA:

- It is caused by **gastrointestinal & renal loss** chloride.
- Gastrointestinal loss occurs by **vomiting** because of **loss of bicarbonate**.
- Renal loss occurs in **Addison's disease** and salt **losing nephropathy.**

HYPERCHLOREMIA

- An **increase in serum chloride level** may be due to

i. Dehydration,

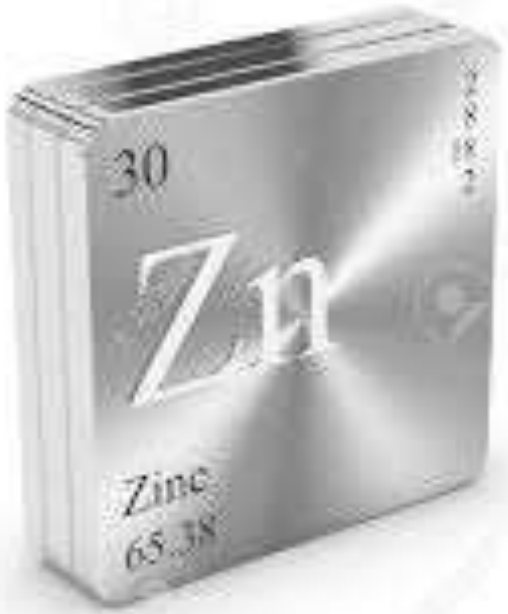
ii. Cushing's syndrome,

iii. Hyperaldosteronism,

iv. Severe diarrhoea (loss of bicarbonate)

v. Respiratory acidosis

ZINC METABOLISM



- Zinc is a **micro mineral.**
- Total body content of zinc**: 2 gm.**
- **Prostate gland** is very rich in Zn.
- Zn is mainly an **intracellular element**.
- **60%** of zinc is present in **skeletal muscle** and **30%** in **bones.**
- It is also present in **liver, brain & skin.**

- **Sources:**

  Meat, liver, milk, dairy products, legumes, pulses, nuts, beans & spinach.

- **RDA:**

Adults: 15 mg/day.

Pregnancy & lactation: 15-20 mg/day.

ABSORPTION

- From **duodenum.**
- It requires a transport protein – **matallo-thionein.**
- **Phytates, Ca^{2+}, copper & iron** decreases zinc absorption.
- **Small peptides & amino acids** promotes zinc absorption.

BIOCHEMICAL FUNCTIONS

- Zinc is component of many metalloenzymes.
  - **Carbonic anhydrase**
  - **Alkaline phosphatase**
  - **Alcohol dehydrogenase**
  - **Lactate dehydrogenase**
  - **Carboxy-peptidase**
  - **Superoxidase dismutase (cytosol) – anti-oxidant**
  - **DNA and RNA polymerases**

- Zn is necessary for
  - Storage & secretion of insulin
  - To maintain normal levels of vitamin A.
  - Synthesis of RBP.
  - Proper reproduction, growth & division of cells
  - Important element in wound healing.
  - Stabilizes protein, nucleic acids & membrane structure.
  - Gusten, a zinc containing protein of the saliva, is important for taste sensation

- **Normal plasma level**: 100 mg/dl

Deficiency:

- **Causes:**

1. Dietary deficiency
2. Malabsorption
3. Chronic alcoholism

- **Symptoms:**

1. Impaired spermatogenesis
2. Growth failure
3. Loss of taste sensation
4. Impaired wound healing
5. Skin lesions such as dermatitis

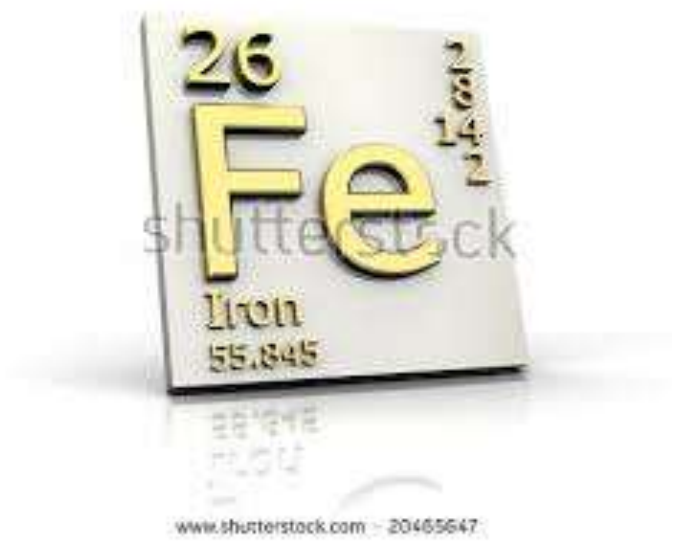
ACRODERMATITIS ENTEROPATHICA:

- A rare **inherited metabolic disease** of zinc deficiency.
- Caused by **defective absorption** of Zn in the intestine.
- Characterized by **inflammation** around mouth, nose, fingers, diarrhea & alopecia (loss of hair in discrete areas)

Zinc Toxicity

- Zinc toxicity is **rare**.
- Seen **in welders due to inhalation** of zinc oxide fumes
- **Clinical features:**
  1. Nausea
  2. Gastric ulcer
  3. Pancreatitis
  4. Diarrhea
  5. Anemia
  6. Excessive salivation

IRON METABOLISM



IRON

Sources

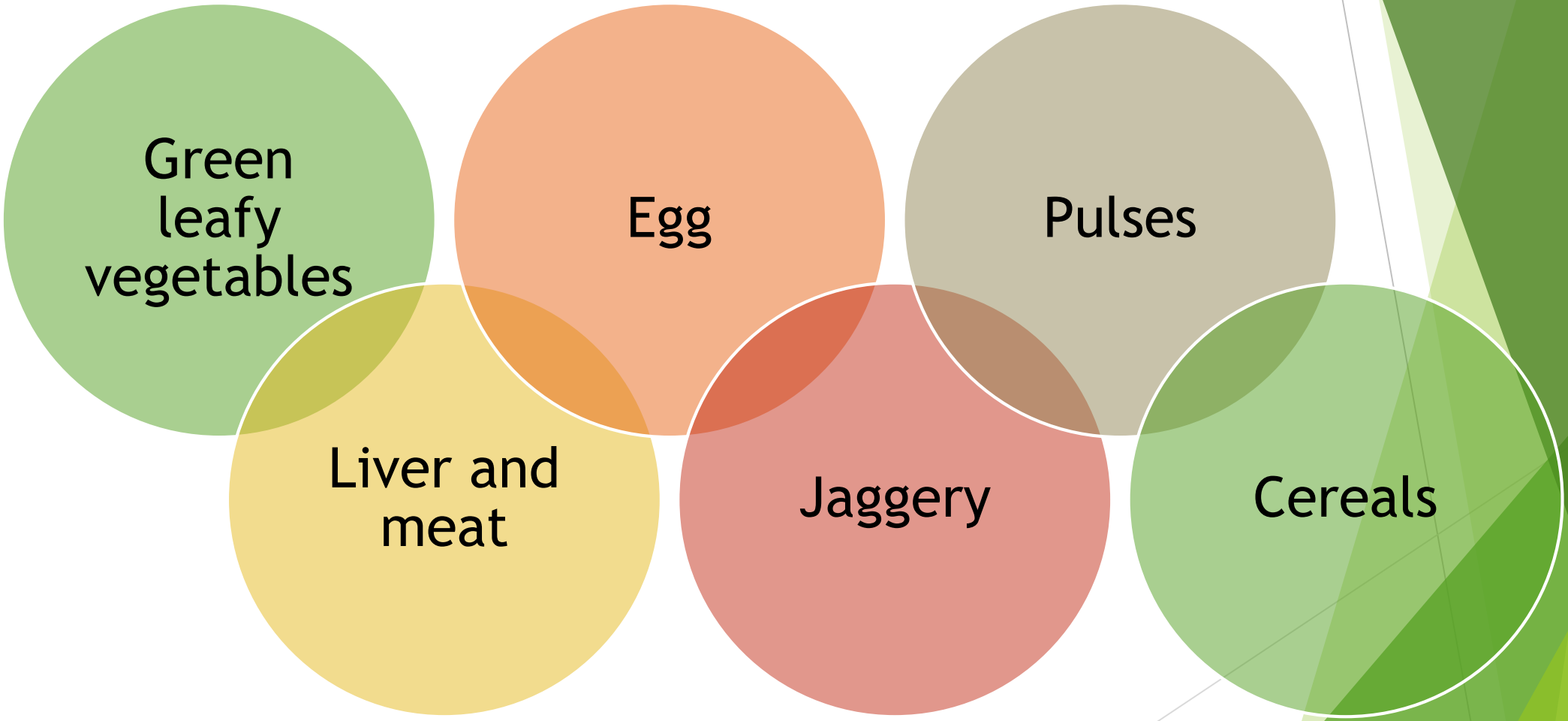
RDA

Metabolism

Functions

Disorders

IRON - SOURCES



IRON - RDA

Adult

10-20 mg/day

Pregnancy

40mg/day

IRON – METABOLISM

IRON - ABSORPTION

Site

Small intestine

Forms

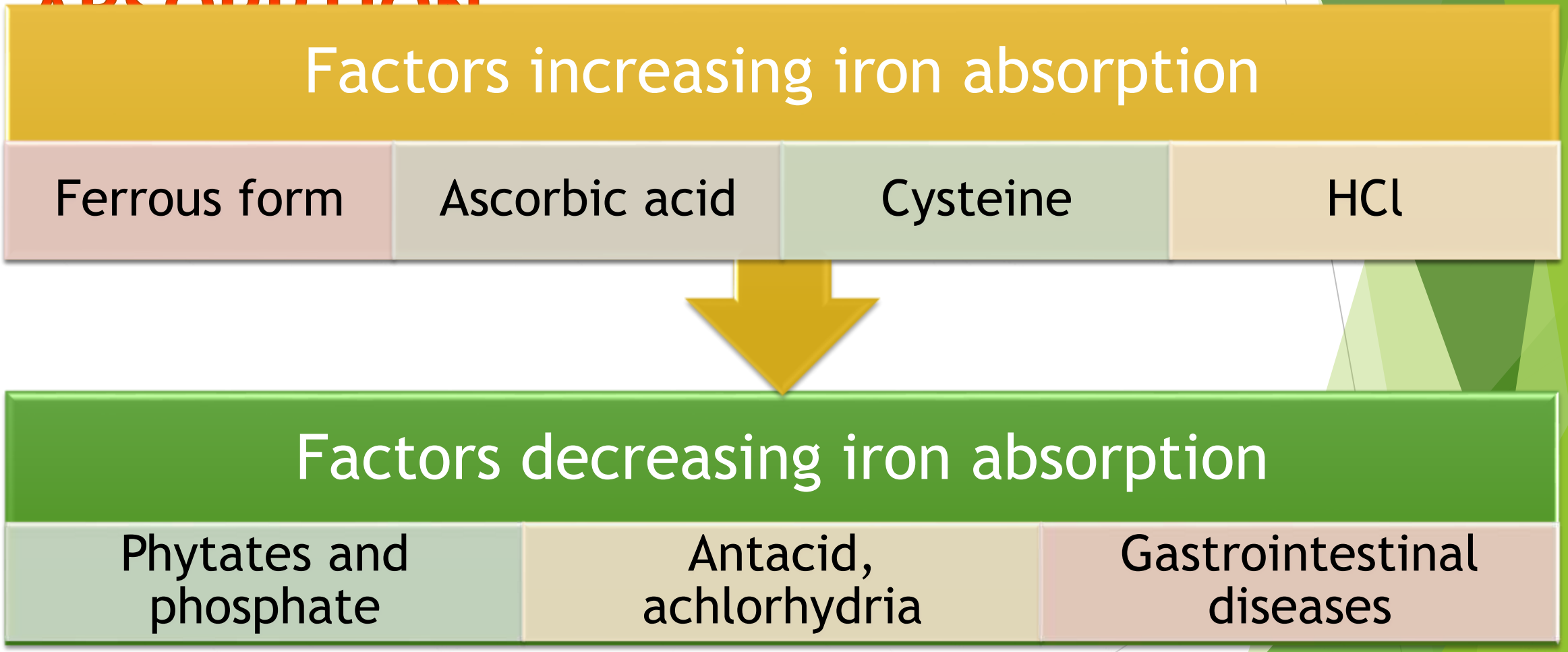
Heme

Non-haem

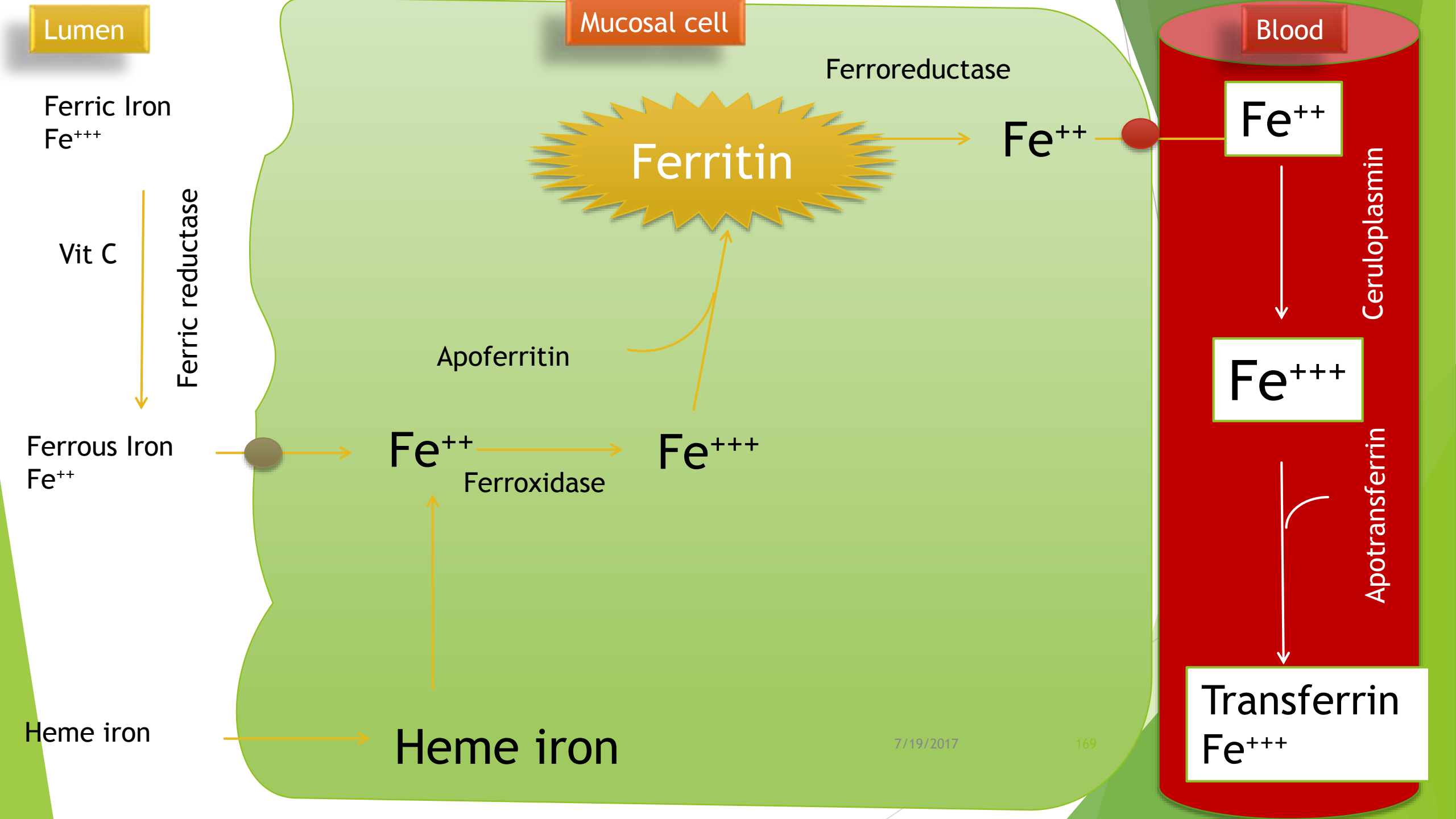
Efficiency

About 10% of total food iron is absorbed

FACTORS AFFECTING IRON ABSORPTION



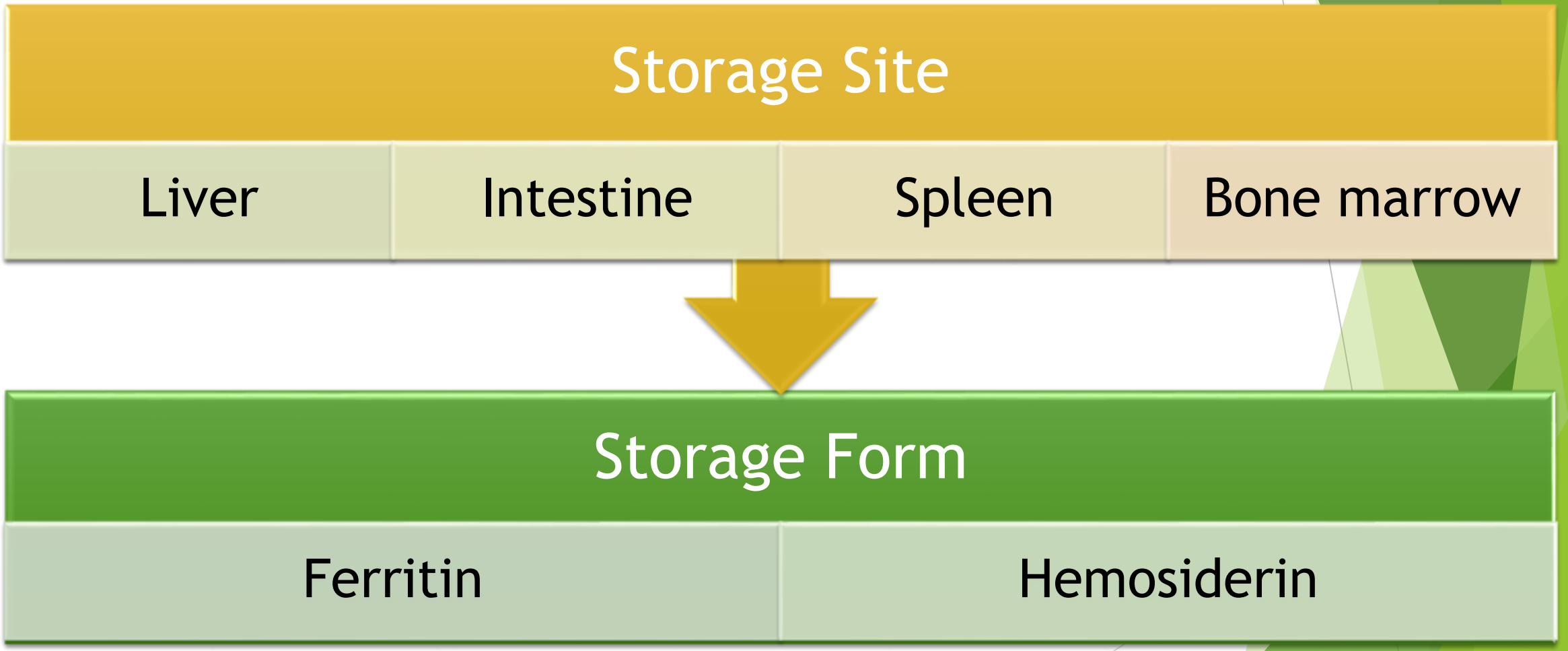
MECHANISM OF IRON ABSORPTION


Lumen
Mucosal cell
Blood
Ferric Iron
Fe+++
Vit C
Ferric reductase
Ferroreductase
Ferritin
Fe++
Fe++
Ceruloplasmin
Apoferritin
Fe+++
Ferrous Iron
Fe++
Fe++
Ferroxidase
Fe+++
Apotransferrin
Transferrin
Fe+++
Heme iron
Heme iron

REGULATION OF IRON ABSORPTION

Mucosal block theory

STORAGE OF IRON



EXCRETION OF IRON

Normal excretion

- Very little
- About 1mg/day

Stool

- 0.7mg/day

Physiological loss

- Menstruation 20-30mg/cycle
- Delivery 750mg

FUNCTIONS OF IRON

Iron is a component of several functionally important compounds

Heme compounds

Non-haem compounds

FUNCTIONS OF IRON

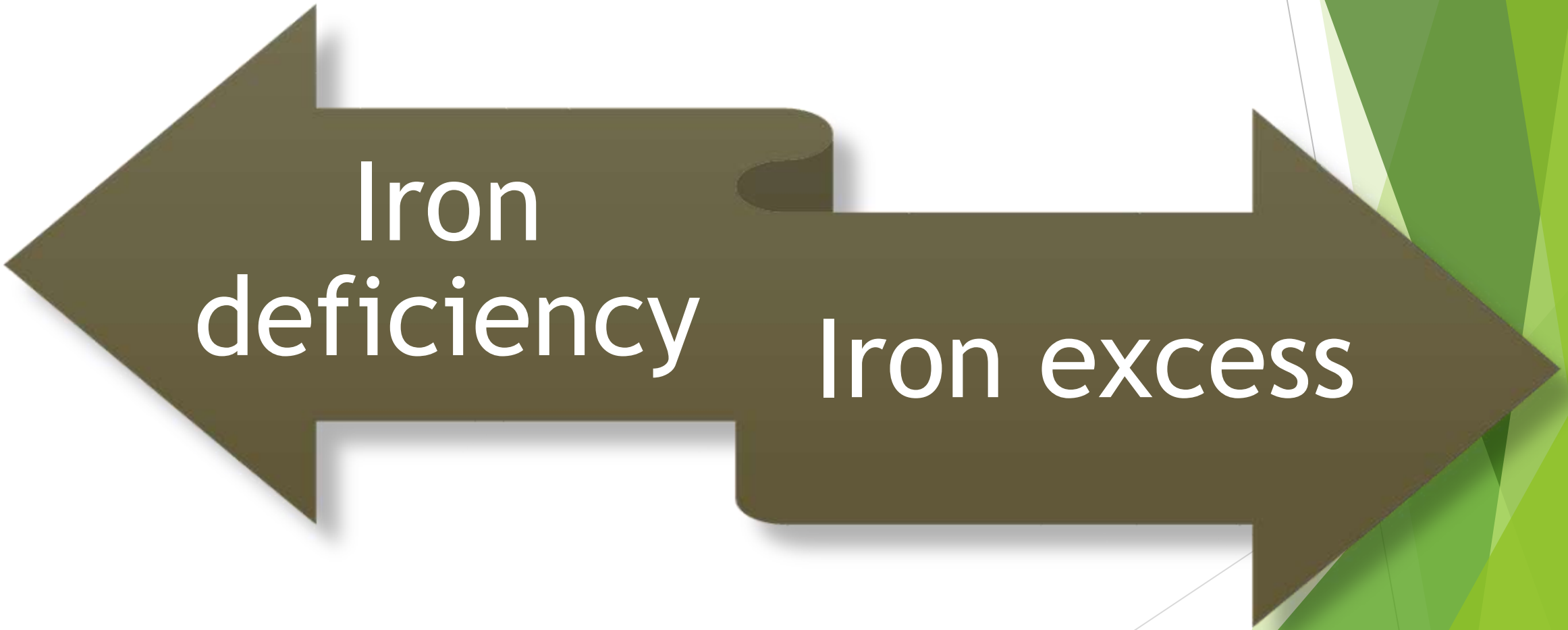
Haem compounds

- Haemoglobin
- Myoglobin
- Cytochrome
- Catalase

Non-haem compounds

- Succinate dehydrogenase
- Xanthine oxidase
- Iron sulfur proteins

DISORDERS OF IRON METABOLISM

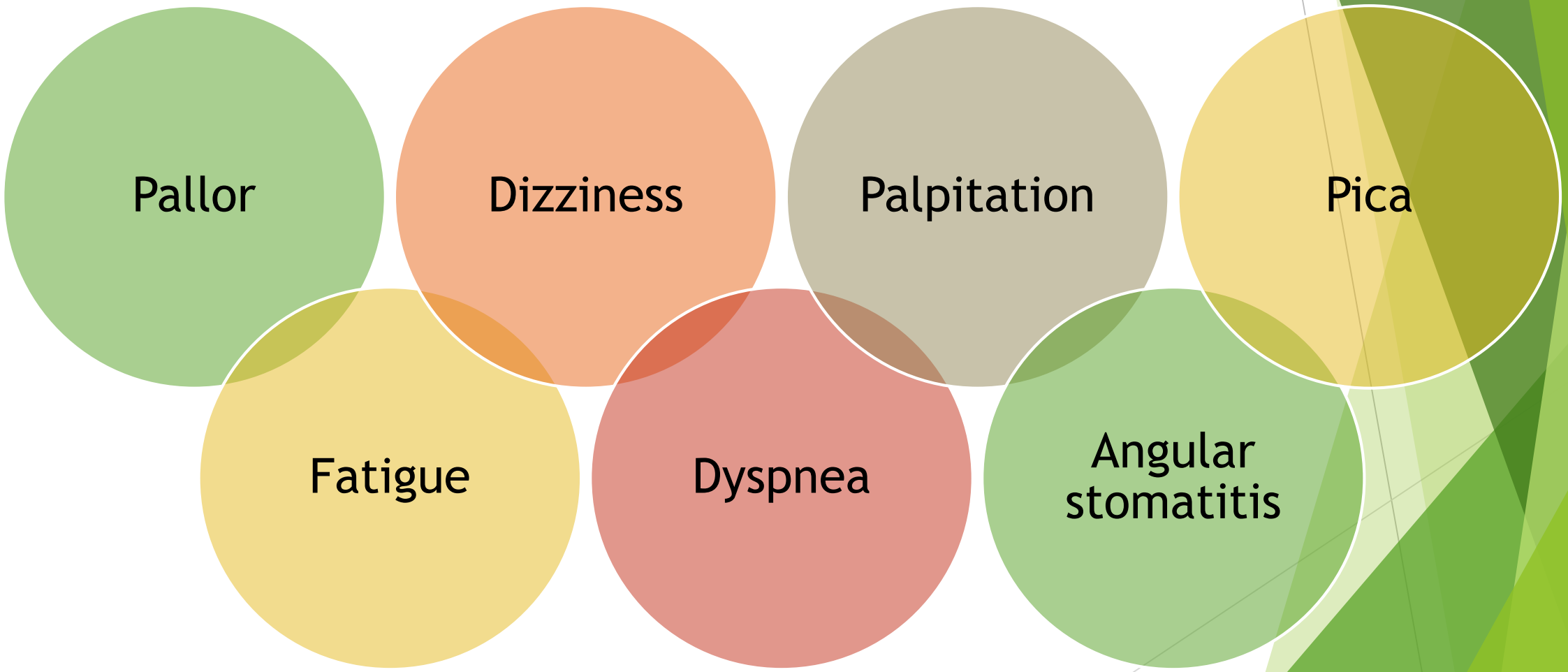


IRON DEFICIENCY ANEMIA

IRON DEFICIENCY - CAUSES

Decreased intake of iron	Decreased absorption of iron	Increased loss of Iron	Increased iron requirement
Malnutrition	Achlorhydria and chronic diarrhea	Bleeding, hookworm infestation	Pregnancy, infancy

IRON DEFICIENCY – FEATURES



IRON DEFICIENCY – LAB FINDINGS

Hematological findings	Decreased hemoglobin
	Microcytic hypochromic anemia
Biochemical findings	Decreased serum iron
	Increased serum total iron binding capacity
	Decreased plasma ferritin

IRON DEFICIENCY – TREATMENT

Treatment of underlying causes

- Treating Hookworm
- Controlling bleeding

Administration of iron preparations

- Orally
- I.V

IRON OVERLOAD

Haemosiderosis

- Increase in iron stores as haemosiderin
- Without associated with tissue injury

Haemochromatosis

- Excessive deposition of iron in the tissue
- Associated with tissue injury

thank you!