VITAMINS

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LEARNING OBJECTIVES

- Define and classify vitamins.
- Differentiate between Fat soluble and Water soluble vitamins.
- Learn each vitamin under the following headings:
- Structure
- Active form
- Functions
- Deficiency disorder
- Sources
- RDA
- Toxicity

VITAMINS

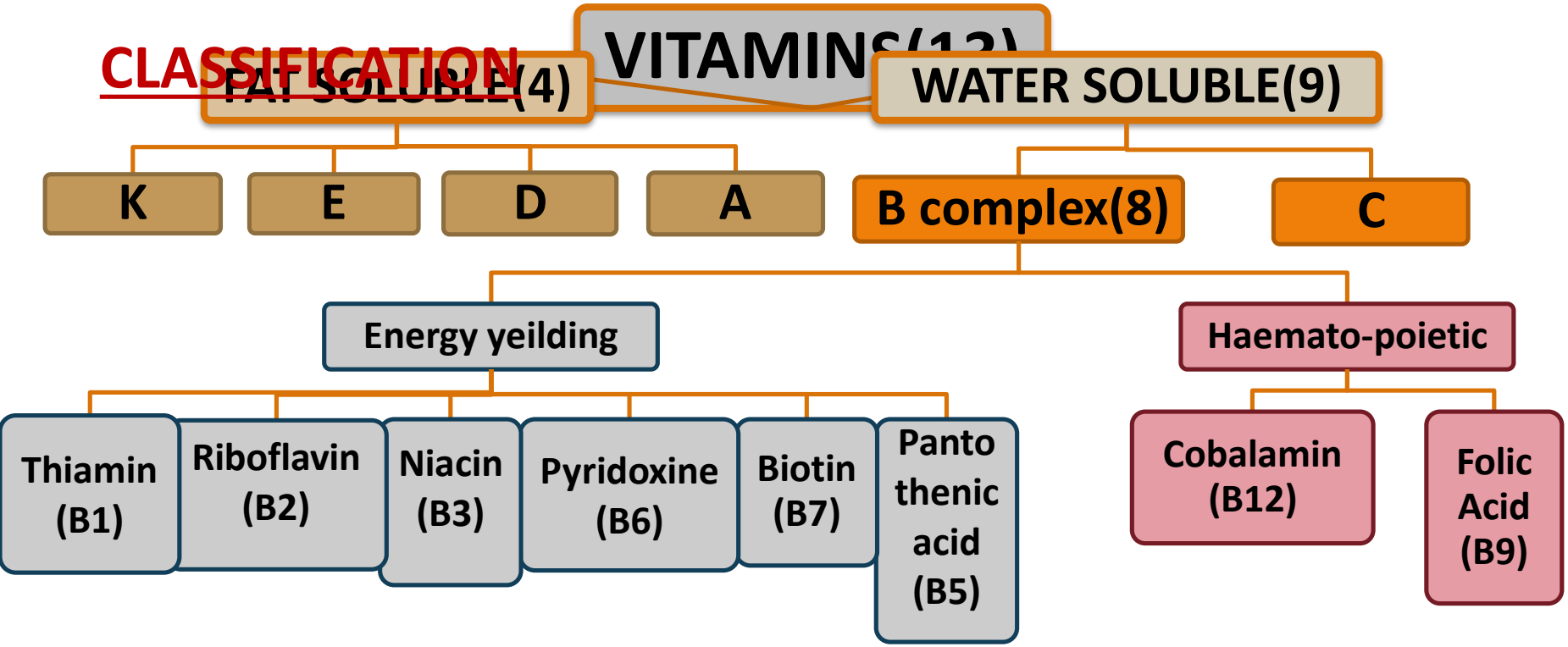
DEFINITION: Vitamins are chemically unrelated organic compounds, required in **small** quantities for a variety of biochemical functions, **cannot** be synthesized in adequate quantities and, therefore, must be taken in the **diet.**

- Macronutrients/Micronutrients
- Degradation of vit?? Metabolic reactions catalyzed which give energy

- Vitamins are required to perform **specific** cellular functions:
- Coenzymes
- Antioxidants
- Vision
- Calcium homeostasis, etc.

- Deficiency is associated with disorders

CLASSIFICATION



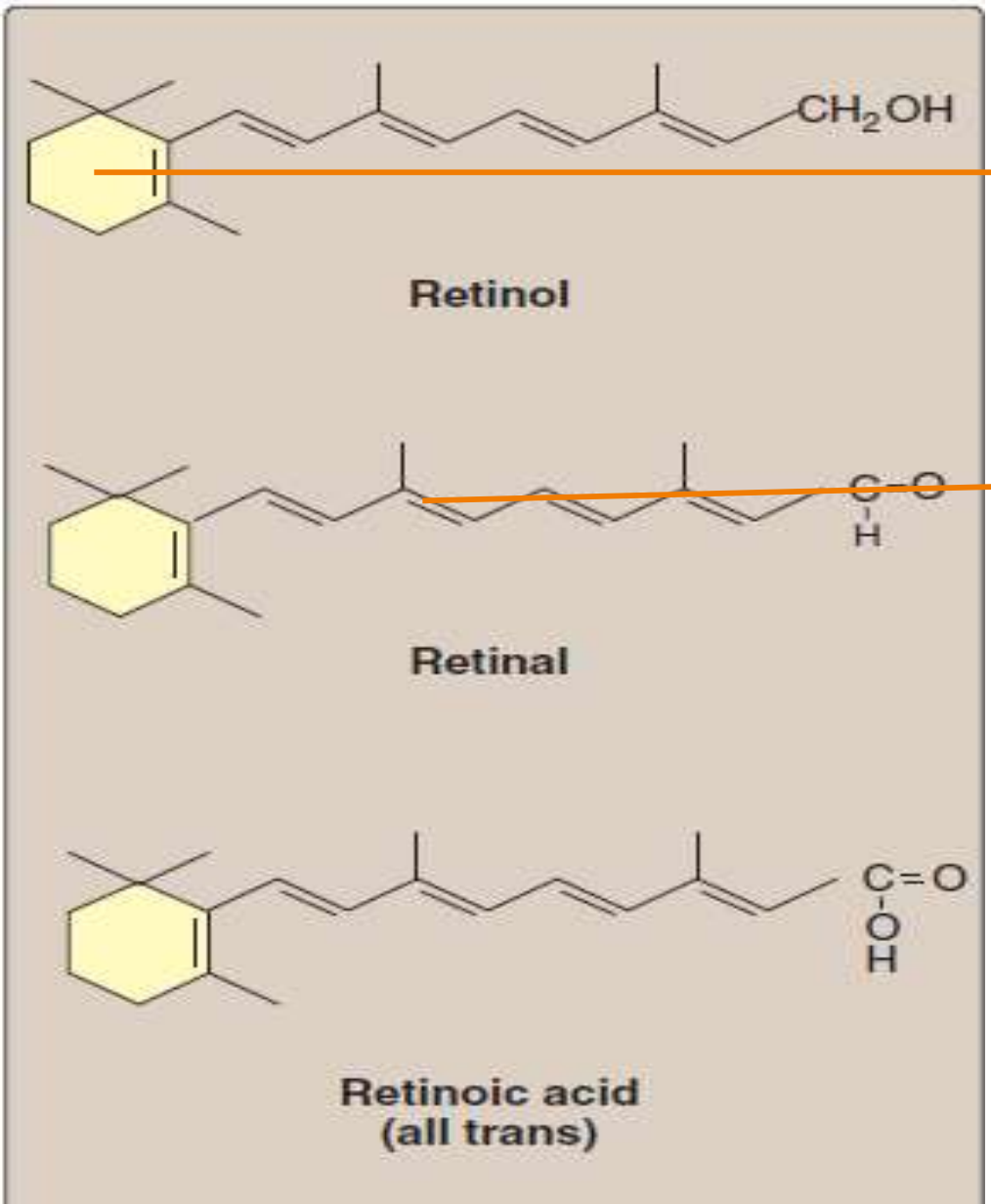
	Fat soluble vitamins	Water soluble vitamins
Solubility in fat	Soluble	Not soluble
Water solubility	Not soluble	Soluble
Absorption	Along with lipids Requires bile salts	*Absorption simple
Carrier proteins	Present	*No carrier proteins
Storage	Stored in liver	*No storage
Excretion	Not excreted	Excreted
Deficiency	Manifests only when stores are depleted	*Manifests rapidly as there is no storage
Toxicity	Hypervitaminosis may result	Unlikely, since excess is excreted
Treatment of deficiency	Single large doses may prevent deficiency	Regular dietary supply is required
Major vitamins	A,D,E and K	B and C

*Vitamin B_{12} is an exception.

FAT SOLUBLE VITAMINS

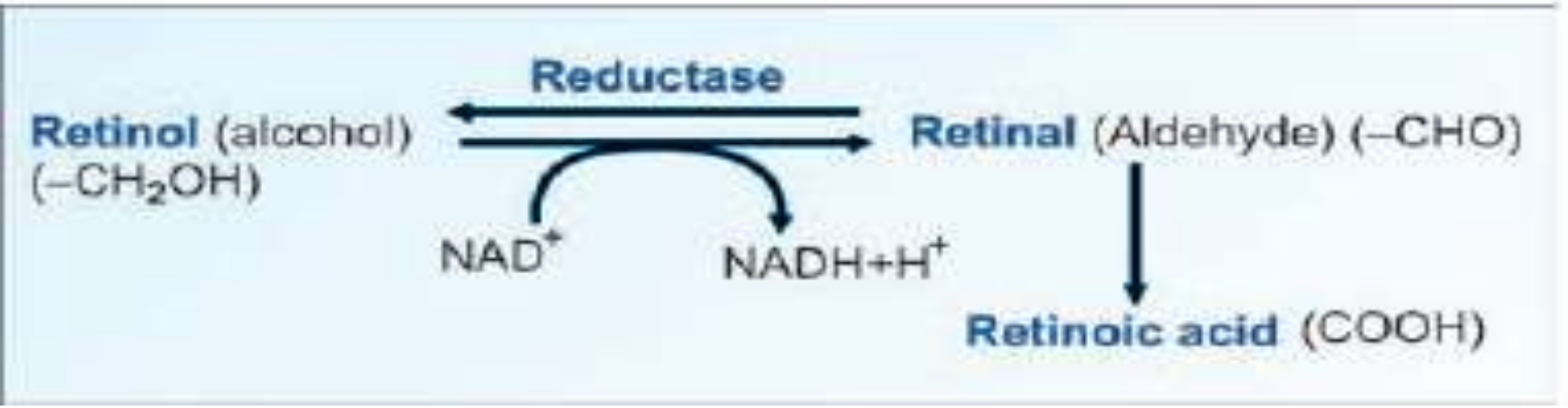
Vitamin A, D, E, K

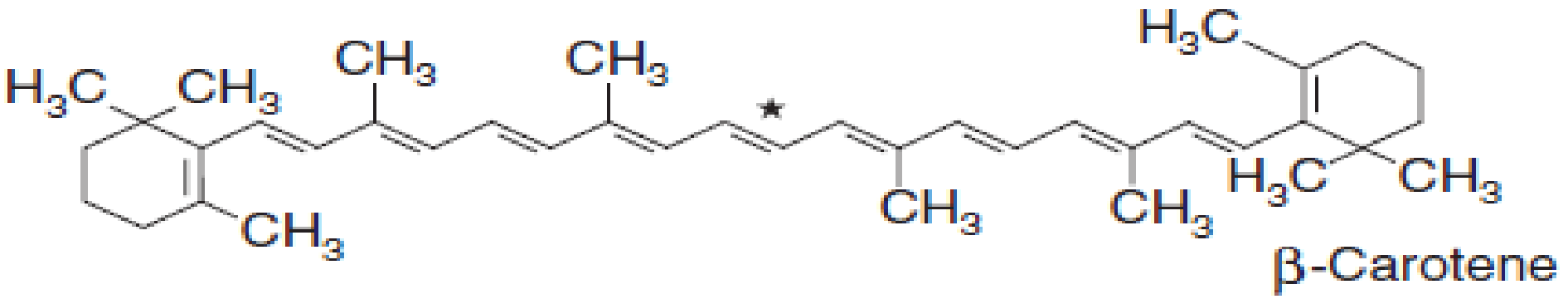
Vitamin A – Structure & Active Forms



Trimethyl cyclohexenyl (β-ionone) ring

Polyisoprenoid side chain





β-Carotene

β-Carotene: **Plant foods contain β-carotene, which can be oxidatively** cleaved in the intestine to yield two molecules of retinal. In humans, the conversion is inefficient, and the vitamin A activity of β-carotene is only about 1/12 that of retinol.

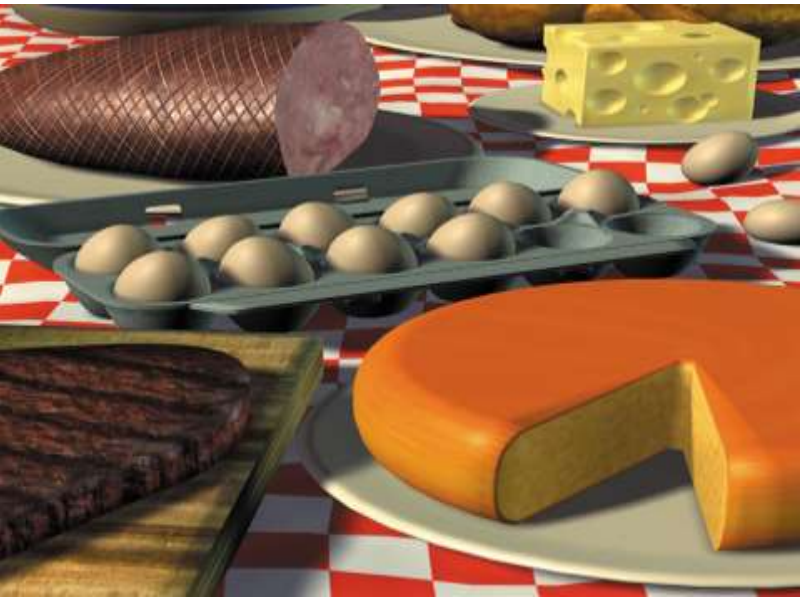
Sources

Animal

- Cod/Shark liver oil
- Egg yolk
- Milk

Plant

- Yellow/orange fruits
- Green vegetables

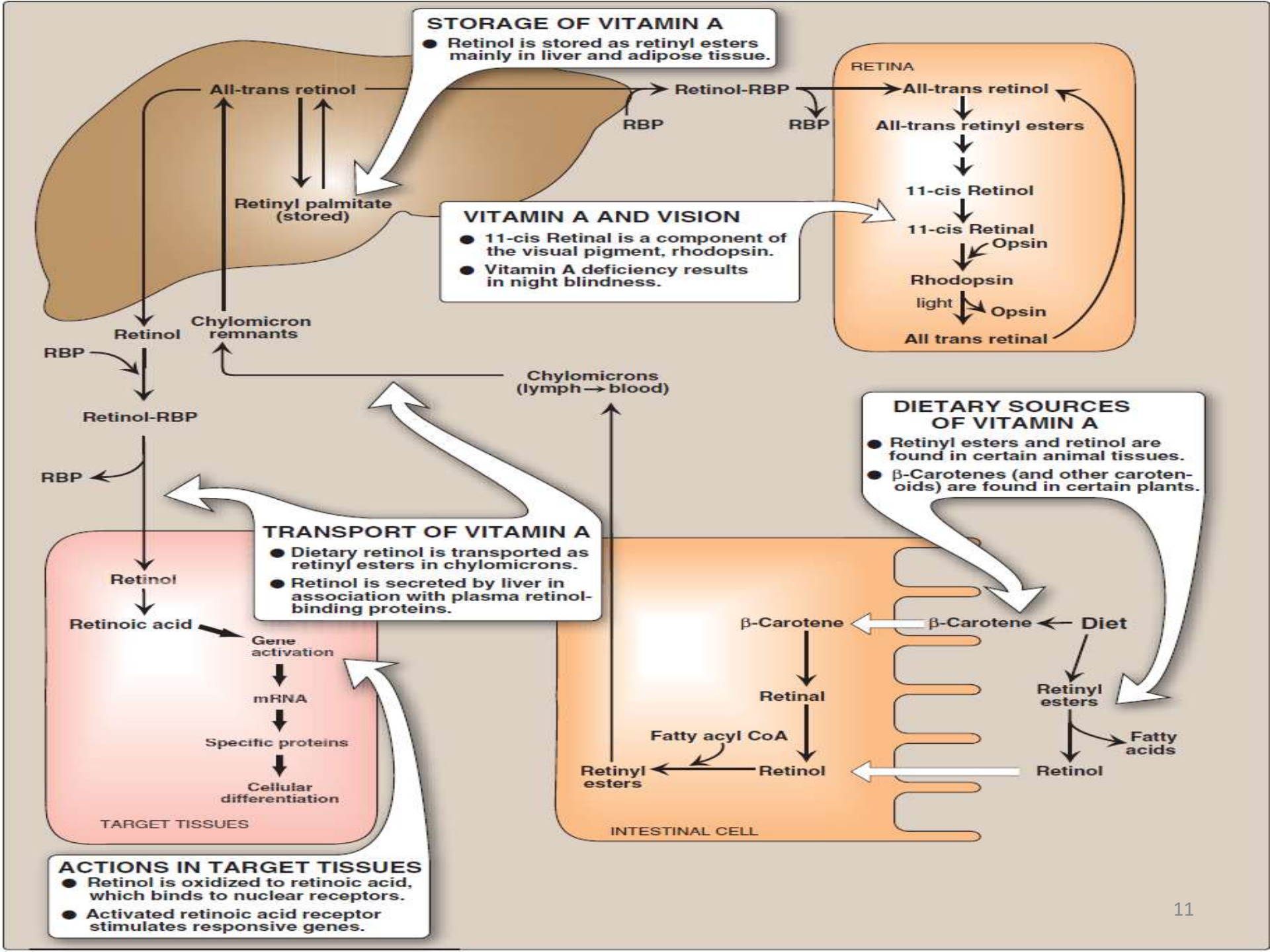


RDA

- Males- 900 RAE (retinol activity equivalents)
- Females- 700 RAE
- 1 RAE = 1 µg of retinol,

  12 µg of β-carotene, or

  24 µg of other carotenoids.


STORAGE OF VITAMIN A
Retinol is stored as retinyl esters mainly in liver and adipose tissue.
All-trans retinol
Retinol-RBP
RBP
RBP
Retinyl palmitate (stored)
RETINA
All-trans retinol
All-trans retinyl esters
11-cis Retinol
11-cis Retinal
Opsin
Rhodopsin
light
Opsin
All trans retinal
VITAMIN A AND VISION
11-cis Retinal is a component of the visual pigment, rhodopsin.
Vitamin A deficiency results in night blindness.
Retinol
RBP
Chylomicron remnants
Chylomicrons (lymph → blood)
Retinol-RBP
RBP
DIETARY SOURCES OF VITAMIN A
Retinyl esters and retinol are found in certain animal tissues.
β-Carotenes (and other carotenoids) are found in certain plants.
TRANSPORT OF VITAMIN A
Dietary retinol is transported as retinyl esters in chylomicrons.
Retinol is secreted by liver in association with plasma retinol-binding proteins.
Retinol
Retinoic acid
Gene activation
mRNA
Specific proteins
Cellular differentiation
TARGET TISSUES
β-Carotene
β-Carotene
Diet
Retinal
Retinyl esters
Fatty acids
Fatty acyl CoA
Retinyl esters
Retinol
Retinol
INTESTINAL CELL
ACTIONS IN TARGET TISSUES
Retinol is oxidized to retinoic acid, which binds to nuclear receptors.
Activated retinoic acid receptor stimulates responsive genes.

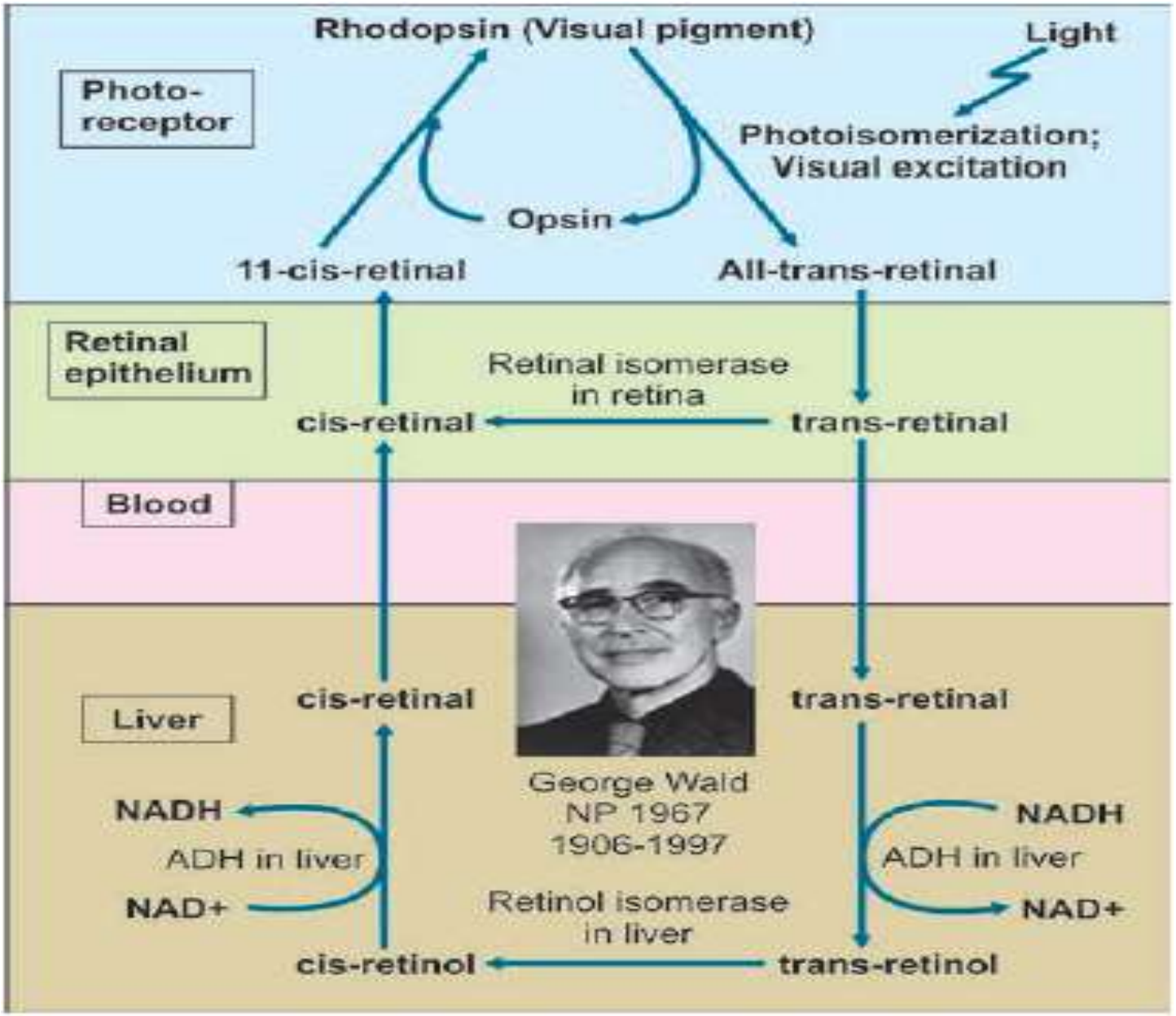
FUNCTIONS OF VITAMIN A

- Vision
- Gene expression and tissue differentiation
- Glycoprotein synthesis
- Reproduction
- Antioxidant role

ROLE IN VISION

- **Rhodopsin,** the visual pigment of the rod cells in the retina, consists of **11-cis retinal** bound to the protein **opsin.**
- When rhodopsin is exposed to **light,** a series of photochemical isomerizations occurs, which results in the bleaching of the visual pigment and release of **all-trans retinal and opsin**.
- This process triggers a **nerve impulse** that is transmitted by the optic nerve to the brain.
- Regeneration of rhodopsin requires isomerization of all-trans retinal back to 11-cis retinal.
- Deficiency of 11 cis-retinal will lead to increase in dark adaptation time and cause night blindness**.**

WALD'S VISUAL CYCLE



FUNCTIONS OF VITAMIN A

Role as steroid hormone: (Retinol and Retinoic Acid)

control gene expression and tissue differentiation

- controls the expression of the gene for keratin in epithelial tissues
- Synthesis of transferrin
- Synthesis of Glycoproteins: component of mucus, required for maintenance of healthy epithelial tissue

Role in Reproduction: (Retinol and retinal)

- spermatogenesis in the male
- preventing fetal resorption in the female.

Antioxidant role of β-carotene

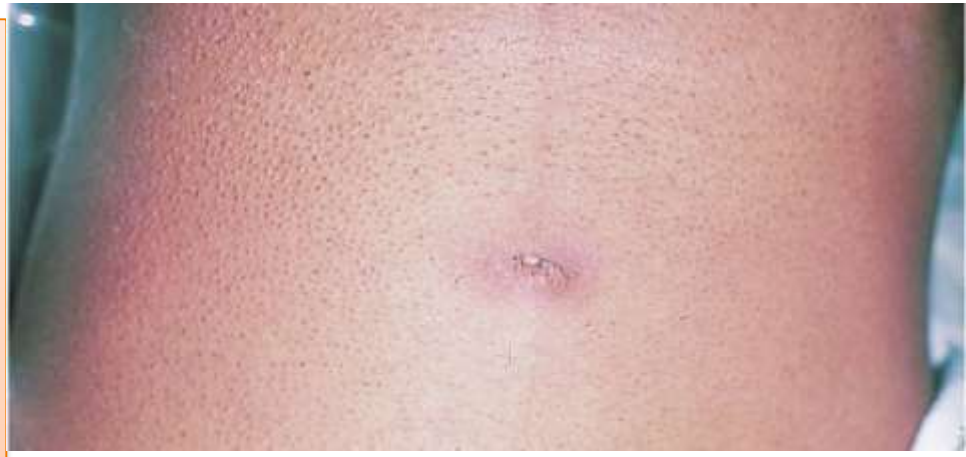
- Increased consumption of β-carotene is associated with decreased incidence of heart attacks, skin and lung cancers.

Deficiency manifestations of Vitamin A

1. Night Blindness or Nyctalopia
2. Xerophthalmia
3. Bitot's Spots
4. Keratomalacia
5. Blindness

Deficiency manifestations of Vitamin A

6. Follicular hyperkeratosis or phrynoderma
7. Keratinization of epithelium
8. Growth retardation
9. Anaemia
10. Infertility
11. Increased susceptibility to infections and cancers.



TOXICITY

- Symptoms of toxicity include
- bone pain,
- scaly dermatitis,
- enlargement of liver and spleen,
- nausea and diarrhoea.

A two and half year old child was brought to the pediatric OPD for episodes of recurrent cough and cold. O/E skin revealed follicular hyperkeratosis and brownish spots at the corner of the eyes.

- This case is related to which vitamin deficiency?
- What are the other clinical manifestations of this vitamin deficiency?
- Give the RDA & sources/ Biochemical functions of this vitamin.

SUMMARY

- Retinal: Vision
- Retinoic acid: Gene expression
  tissue diffrentiation
- Retinol: Reproduction
- Beta-carotene: Antioxidant role

- **Sources & RDA:**
- Fish liver oils
- Egg yolk
- Milk products
- Yellow /green veg
- 900 /700 RAE

Toxicity: yes

Deficiency manifestations

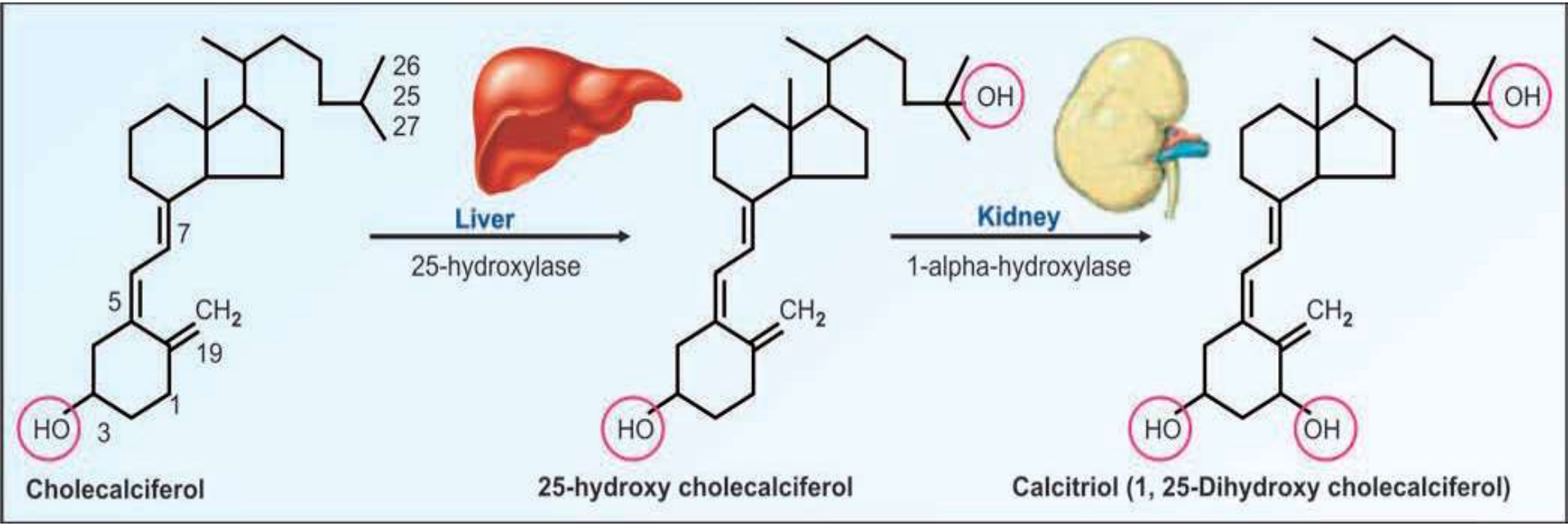
1. Night Blindness or Nyctalopia
2. Xerophthalmia
3. Bitot's Spots
4. Keratomalacia
5. Preventable Blindness
6. Follicular hyperkeratosis or phrynoderma
7. Keratinization of epithelium
8. growth retardation
9. Anaemia
10. Infertility
11. Increased susceptibility to infections and cancers.

VITAMIN D

- **Sunshine vitamin/Antirachitic vitamin**
- Vitamin D is not strictly a vitamin since it **can be synthesized** in the skin.
- **7-Dehydrocholesterol,** an intermediate in cholesterol synthesis, is converted to **cholecalciferol** in the dermis and epidermis when exposed to **sunlight.**
- **Diet** contains preformed vitamin D - Ergocalciferol (D2), found in plants, and cholecalciferol (D3), found in animal sources.
- Preformed vitamin D is a dietary requirement only in individuals with limited exposure to sunlight.

Metabolism of vitamin D

- **Active form: 1,25 dihydroxycholecalciferol/calcitriol**
- **Formation of 1,25-diOH-D3:**



Sources

Fish liver oils and egg yolk.

Milk, unless it is artificially fortified, is not a good source.

RDA

600 IU upto 70 years of age

800 IU after 70 years of age

Functions of vitamin D

- The overall function of **calcitriol** is to maintain adequate plasma levels of **calcium and phosphorus**.
- It performs this function by action on **3 target organs**:

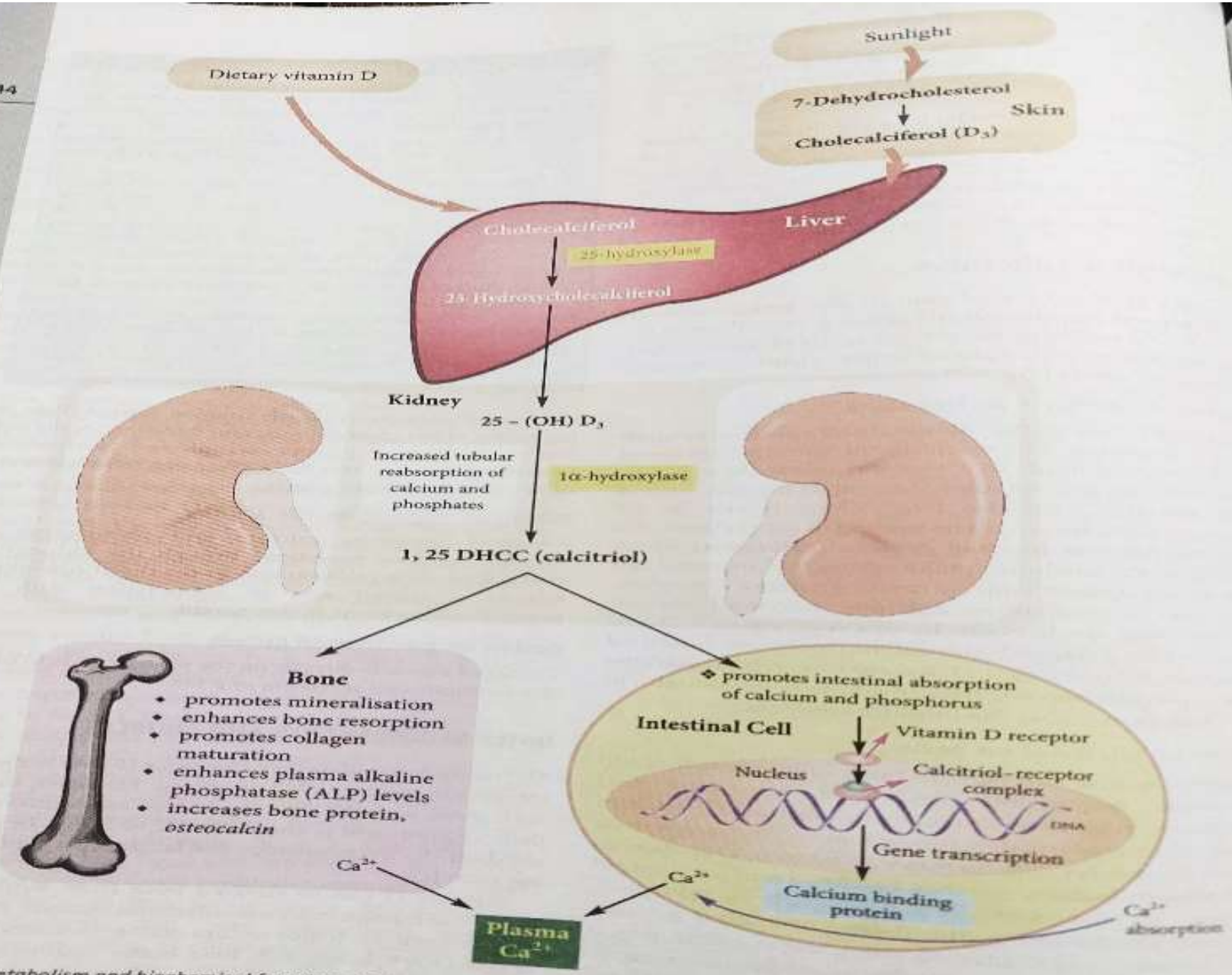
1) intestine - absorption of calcium and phosphorus,

2) kidney - reabsorption of calcium and phosphorus

3) bone – resorption by stimulating osteoclast activity

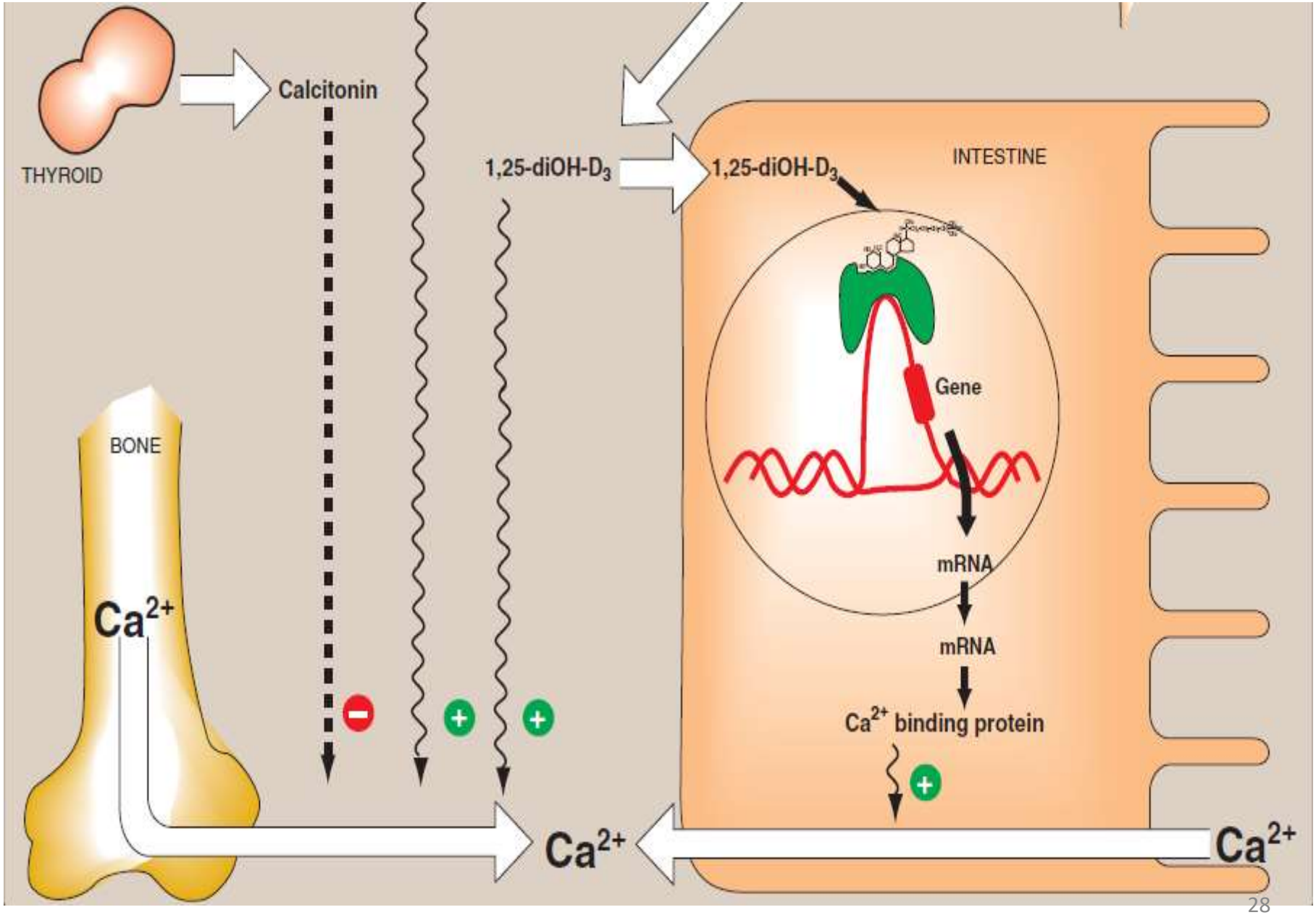
Mineralization stimulating osteoblast activity

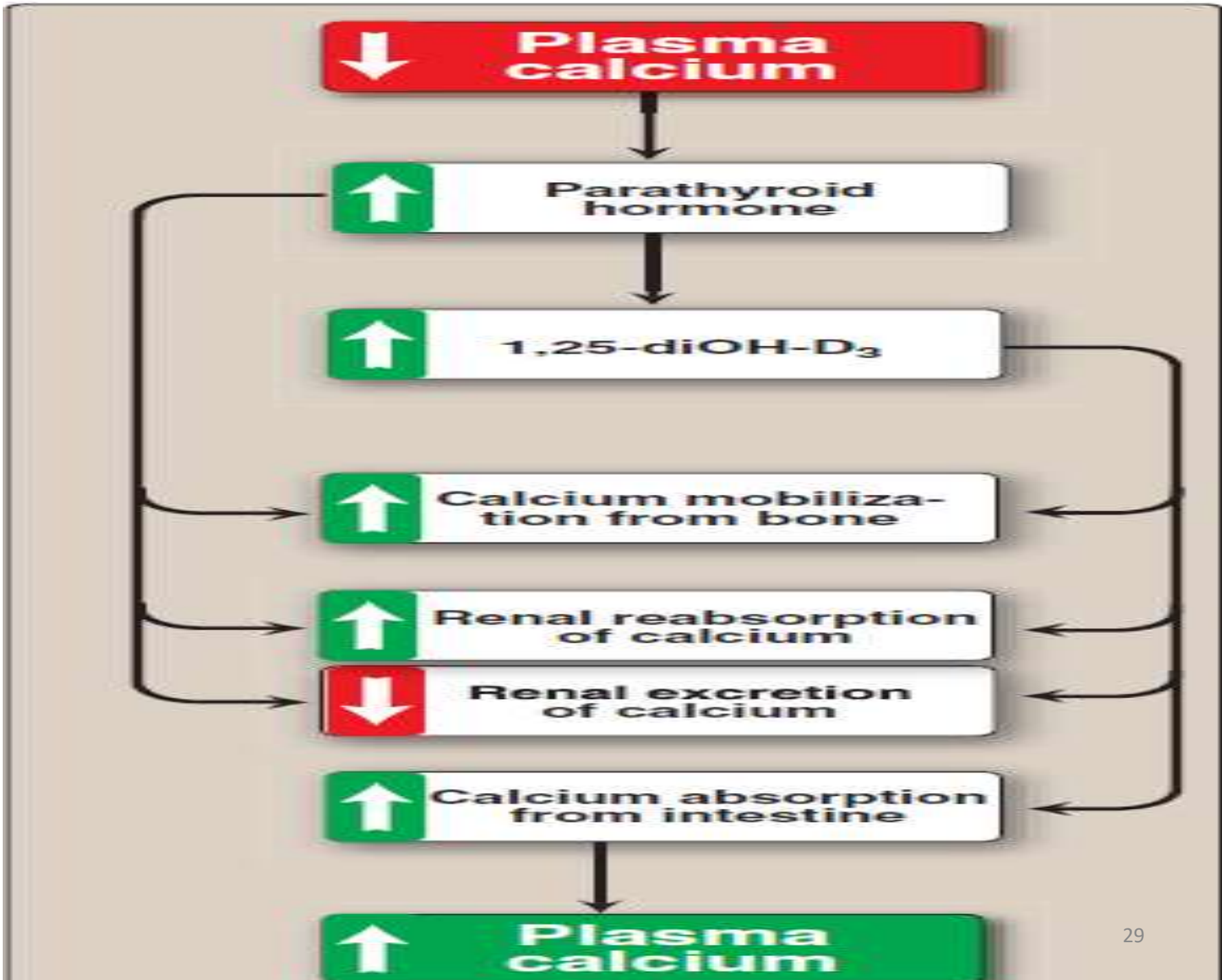
- In its actions, it behaves like a steroid hormone, binding to a nuclear receptor protein, like vitamin A.



g. 8.7 *Metabolism and biochemical functions of vitamin D.*

PTH


THYROID
Calcitonin
1,25-diOH-D3
1,25-diOH-D3
INTESTINE
Gene
mRNA
mRNA
Ca2+ binding protein
BONE
Ca2+
Ca2+
Ca2+

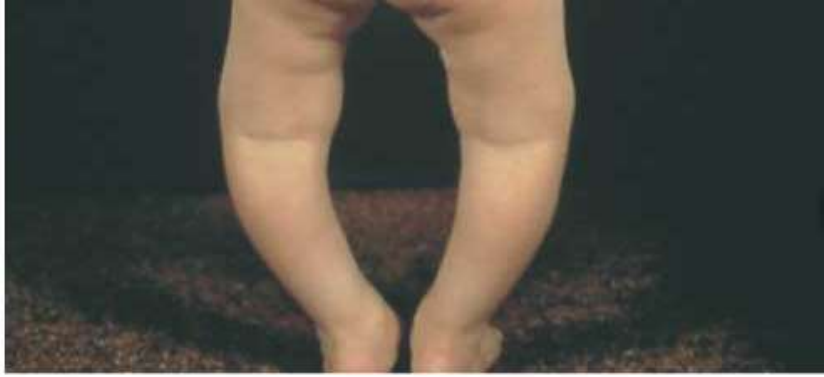

Plasma calcium
Parathyroid hormone
1,25-diOH-D3
Calcium mobiliza-tion from bone
Renal reabsorption of calcium
Renal excretion of calcium
Calcium absorption from intestine
Plasma calcium

Deficiency Manifestations

- The deficiency diseases are
- **rickets in children and**
- **osteomalacia in adults.**
- **Rickets** is characterized by the continued formation of the collagen matrix of bone, but incomplete mineralization, resulting in soft, pliable bones.
- In **osteomalacia**, demineralization of pre-existing bones increases their susceptibility to fracture.
- **Causes:** fat malabsorption, kidney or liver disease, elderly (minimal exposure to sunlight), strict vegetarians, chronic alcoholics and corticosteroid therapy.

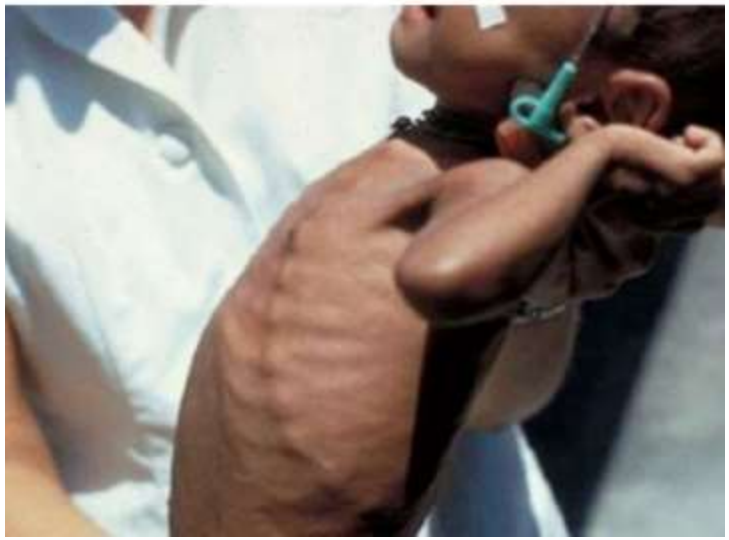
Rickets

- The clinical manifestations include:
- bow legs,
- knock-knee,
- rickety rosary,
- bossing of frontal bones,
- pigeon chest,
- Harrison's sulcus,
- Delayed closure of fontaneles



Bowed legs. In rickets, the poorly formed long bones of the legs bend outward as weight-bearing activities such as walking begin.

Rachitic rosary



Toxicity of vitamin D

- High doses (100,000 IU for weeks or months) can cause loss of appetite, nausea, thirst, and stupor.
- Hypercalcemia can lead to **metastatic calcification or calcinosis -** deposition of calcium in many organs, particularly the arteries and kidneys.
- The UL is 2000 IU/day.

SUMMARY

- **Sunshine/Antirachitic vitamin**
- Can be synthesized in the body from 7-dehydrocholesterol
- **Active form:** Calcitriol/1,25dihydroxycholecalciferol
- **Function:** calcium homeostasis
- **3 target organs:** intestine, bone and kidney
- Acts like a **steroid hormone**
- **Deficiency : Rickets** in children and **Osteomalacia** in adults
- **Sources:** Fish liver oils and egg yolk.
- **RDA:** 15µg/600 IU **upto** 70 years of age
  20µg/800 IU **after** 70 years of age
- **Toxicity: Yes**

A 2 year old child was brought to pediatric OPD with delayed eruption of teeth, bow legs and knock knees. On examination he had rickety rosary and growth retardation.

Lab investigations show: Serum calcium-8.2mg/dl,

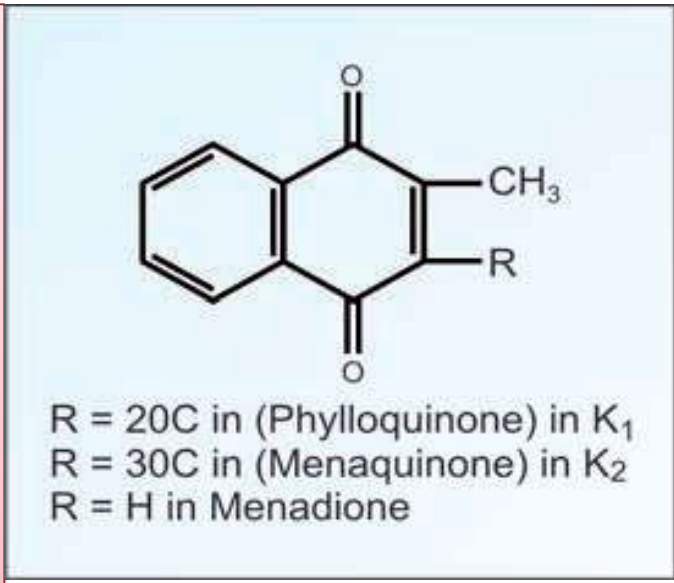
Serum phosphorus-2.8mg/dl

Serum Alkaline phosphatase:720IU/L

- What are the biochemical abnormalities seen in the lab result?
- What is the possible cause?
- Give the RDA & sources/Biochemical functions of this vitamin.

VITAMIN K

- **Structure:** polyisoprenoid substituted naphthoquinone
- **Phylloquinone(K1),**found in green vegetables;
- **menaquinone(K2),**synthesized by intestinal bacteria,
- **menadione, menadiol, and menadiol diacetate,** synthetic compounds that can be metabolized to phylloquinone.



Sources of Vitamin K

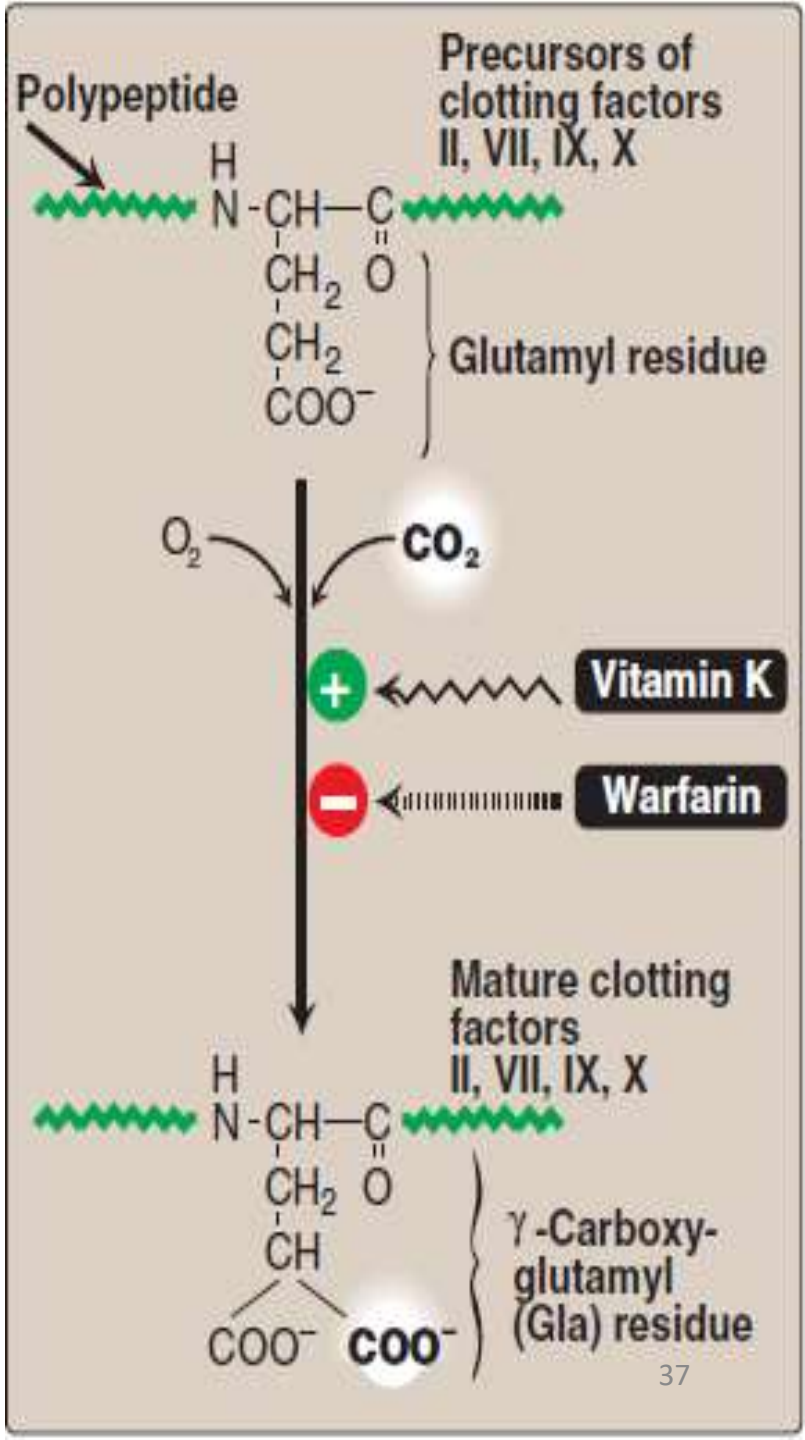
- **Green leafy vegetables are good dietary sources.**
- Even if the diet does not contain the vitamin, intestinal bacterial synthesis will meet the daily requirements, as long as absorption is normal.

- **RDA:**
- 120 µg/day for adult males and
- 90 µg/day for adult females.

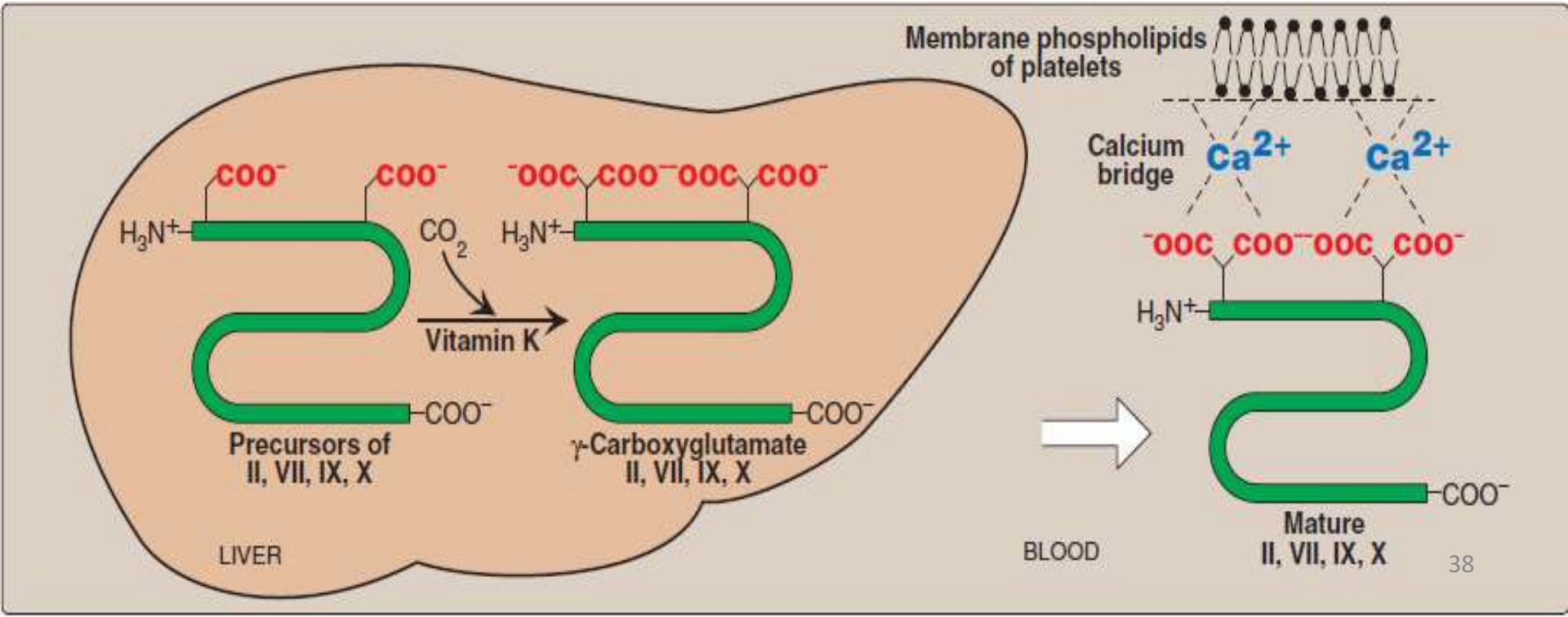
Biochemical Role of Vitamin K

- Coagulation of blood by activation of clotting factors:
- **Factor II (prothrombin);**
- **Factor VII (serum prothrombin conversion accelerator);**
- **Factor IX (Christmas factor);**
- **Factor X (Stuart Prower factor)**

- Vitamin K is the cofactor for the carboxylation of glutamate residues in the post-synthetic modification **(posttranslational modification)** of proteins (blood clotting factors) to form **γ-carboxyglutamate**(Gla), which chelates the calcium ion.

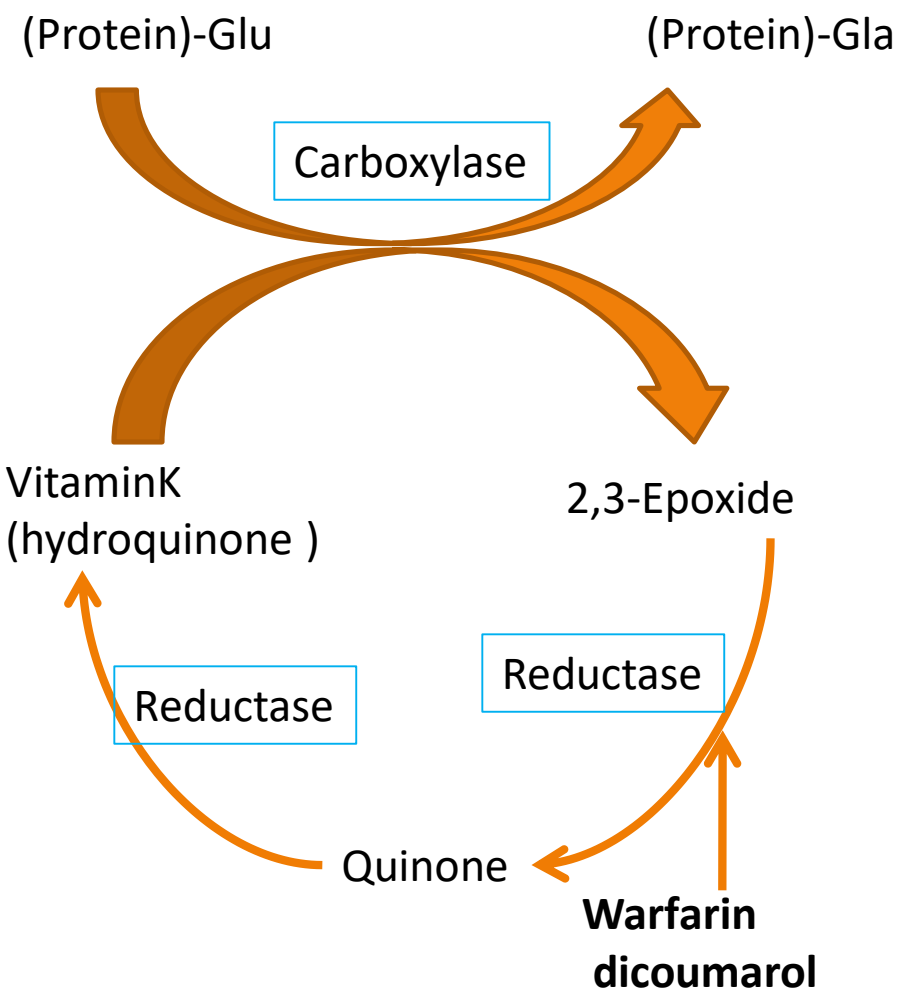


The Gla residues of prothrombin are good **chelators** of positively charged calcium ions, because of the two adjacent, negatively charged carboxylate groups. The prothrombin–calcium complex is then able to bind to phospholipids essential for blood clotting on the surface of platelets. Attachment to the platelet increases the rate at which the proteolytic conversion of prothrombin to thrombin can occur which converts fibrinogen to fibrin.



Biochemical Role of Vitamin K

- **Warfarin and dicoumarol will competitively inhibit** the gamma carboxylation system due to structural similarity with vitamin K. Hence they are widely used as **anticoagulants** for therapeutic purposes.
- Vitamin K dependent gamma carboxylation is also necessary for the functional activity of **osteocalcin** synthesized by osteoblasts. It is required for bone mineralization.
- Activation of cell cycle regulatory proteins-Cyclins is by gamma carboxylation.



Clinical Manifestations of Deficiency

- A true vitamin K deficiency is unusual because adequate amounts are generally produced by intestinal bacteria or obtained from the diet.
- Causes of deficiency:
  - The amount of endogenously formed vitamin is depressed by prolonged use of antibiotics,
  - obstructive jaundice and fat malabsorption
- **Hemorrhagic disease of the newborn** is attributed to vitamin K deficiency. This is due to lack of hepatic stores, limited oral intake (breast milk has very low levels, 15 mg/liter) and absence of intestinal bacterial flora.
- pre-term infants given **prophylactic doses** of vitamin K (1 mg Menadione).

Clinical Manifestations of Deficiency

- In children and adults, Vitamin K deficiency may be manifested as bruising tendency, ecchymotic patches, mucous membrane hemorrhage, post-traumatic bleeding and internal bleeding.
- Prolongation of prothrombin time and delayed clotting time are characteristic of vitamin K deficiency.

Toxicity of vitamin K

- Prolonged administration of large doses of synthetic vitamin K (menadione) can produce hemolytic anemia and jaundice in the infant, due to toxic effects on the membrane of red blood cells.

SUMMARY

- **Vitamin E**
- **Anti-sterility vitamin**
- **α-tocopherol**
- **Function: Antioxidant**
- **Deficiency: Hemolytic anemia**
- **Sources: Vegetable oils**
- **RDA: 15 mg**
- **No toxicity**

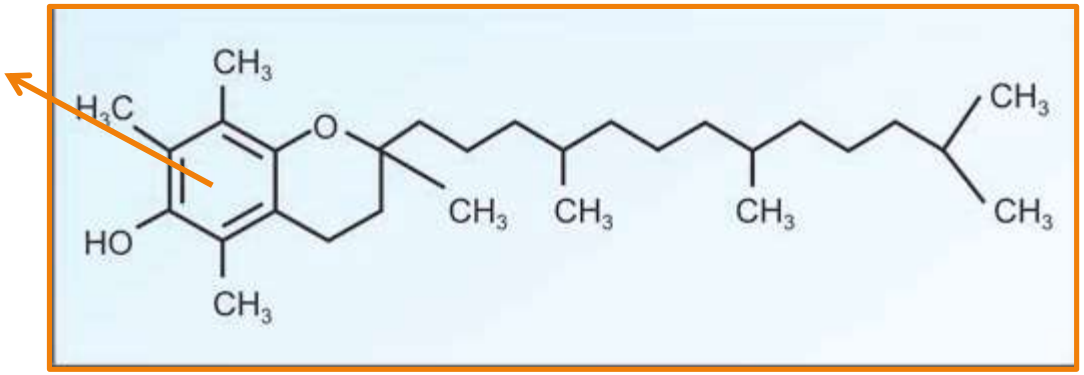
- **Vitamin K**
- **Menadione**
- **Menaquinone**
- **Phylloquinone**

- **Function: γ-Carboxylation of glutamate residue in clotting and other proteins** (II,VII,IX,X, osteocalcin)
- **Deficiency: Bleeding tendency**
- **Sources: Green leafy vegetables**
  Intestinal bacterial synthesis
- **RDA:** 120 µg/day-males
  90 µg/day-females
- **Toxicity:** hemolytic anemia and jaundice

VITAMIN E

- **Anti-sterility vitamin/Tocopherol**
- Consists of eight naturally occurring tocopherols, of which **α-tocopherol** is the most active

6-hydroxy-chromane ring



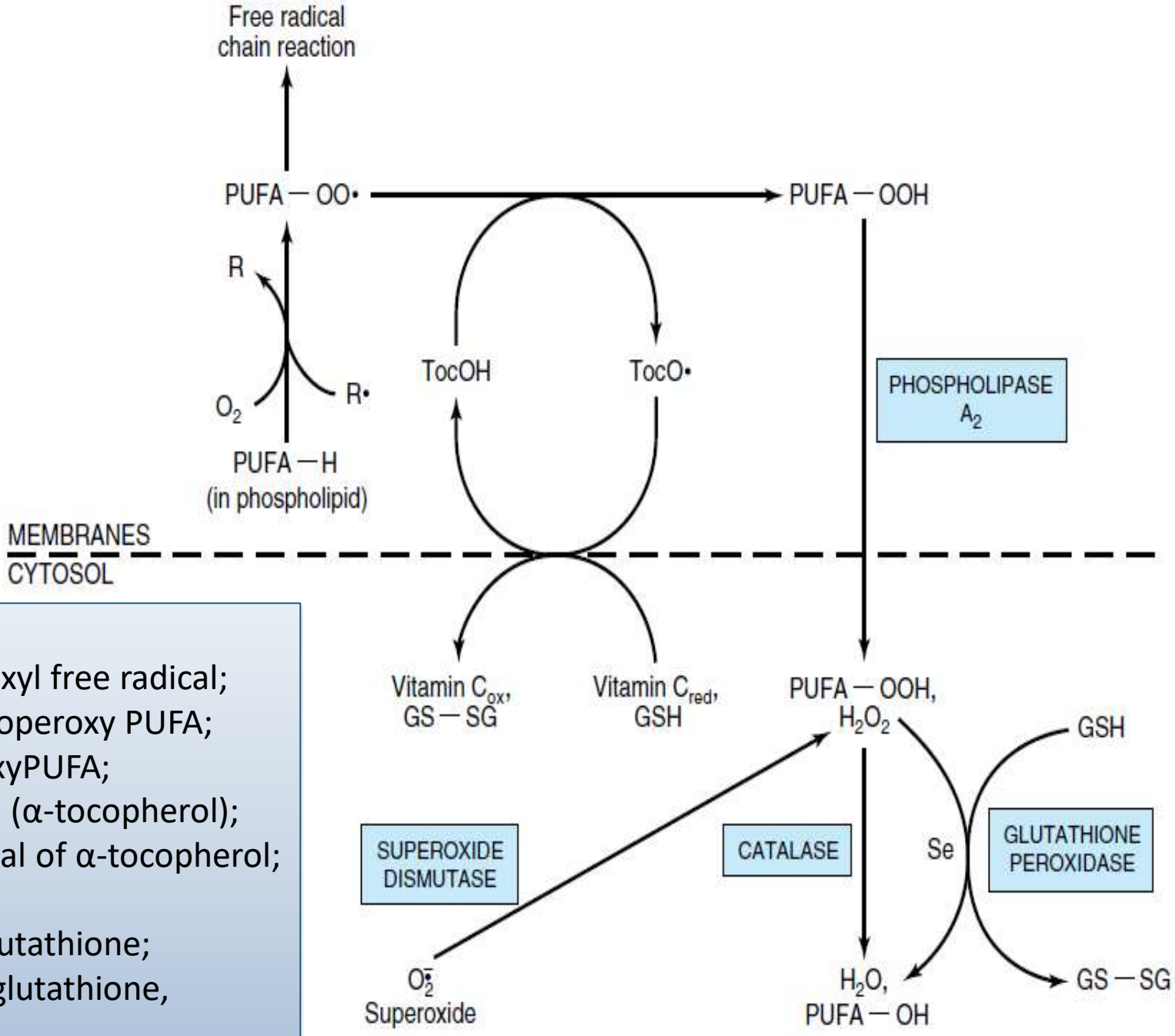
SOURCES & RDA

- **Vegetable oils are rich sources of vitamin E; e.g.** wheat germ oil, sunflower oil, safflower oil, cotton seed oil, etc.
- The RDA for α-tocopherol is **15mg** for adults.
- The vitamin E requirement increases as the intake of polyunsaturated fatty acid increases.

- **Toxicity of vitamin E**
- Vitamin E is the least toxic of the fat-soluble vitamins, and no toxicity has been observed at doses of 300 mg/day.

BIOCHEMICAL ROLE

- The main function of vitamin E is as a chain-breaking, free radical trapping **antioxidant** in cell membranes and plasma lipoproteins.
- It reacts with the lipid peroxide radicals formed by peroxidation of polyunsaturated fatty acids before they can establish a chain reaction.
- Hence it prevents **hemolysis,** damage to lysosomal/ mitochondria/ endoplasmic reticulum membrane.
- It helps in slowing the ageing process as gradual deterioration of **ageing process is** due to the cumulative effects of free radicals.
- It reduces the risk of **atherosclerosis** by reducing oxidation of LDL



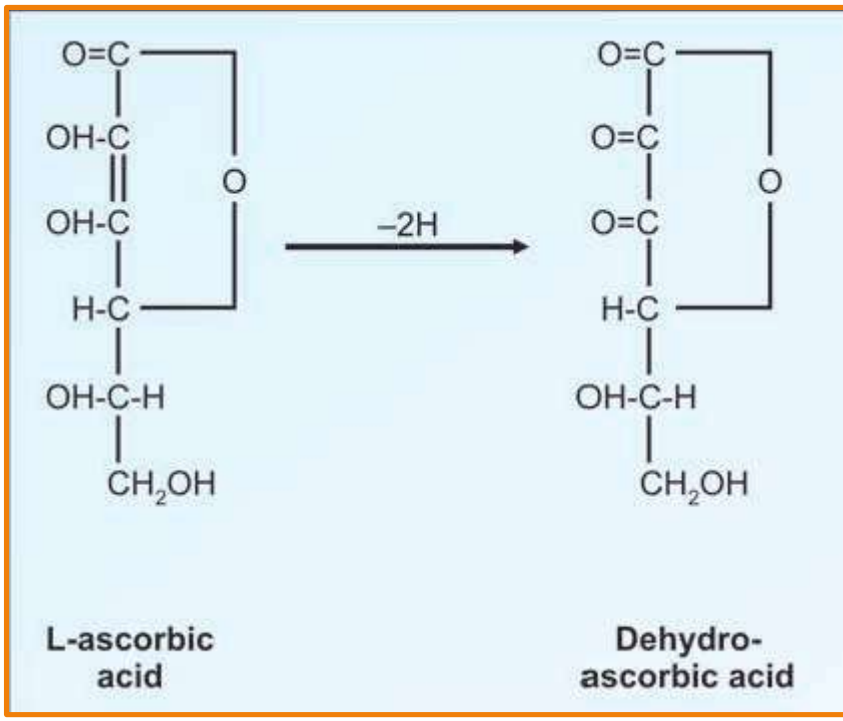
(R•, free radical;
PUFA-OO•, peroxyl free radical;
PUFA-OOH, hydroperoxy PUFA;
PUFA-OH, hydroxyPUFA;
TocOH,vitamin E (α-tocopherol);
TocO•, free radical of α-tocopherol;
Se, selenium;
GSH, reduced glutathione;
GS-SG, oxidized glutathione,
PUFA-H, PUFA.)

Deficiency Manifestations

- Vitamin E deficiency is almost entirely restricted to premature infants.
- When observed in adults, it is usually associated with defective lipid absorption or transport.
- Erythrocyte membranes are abnormally fragile as a result of peroxidation, which leads to **hemolytic anemia**.
- In experimental animals, vitamin E deficiency results in resorption of fetuses and testicular atrophy.

ASCORBIC ACID
(Vitamin C/Anti-scorbutic Factor)

- **Structure:** resembles glucose
- Only L-ascorbic acid and dehydroascorbic acid have antiscorbutic activity.
- The D-ascorbic acid has no activity.
- Ascorbic acid is partly excreted unchanged and partly as oxalic acid.



ASCORBIC ACID

Biochemical Role: as a **coenzyme** in following reactions:

1. Hydroxylation of prolyl and lysyl residues of **collagen.** Vitamin C is, therefore, required for the maintenance of normal connective tissue, as well as for wound healing.
2. *Dopamine-hydroxylase* is a copper-containing enzyme involved in the synthesis of the catecholamines **norepinephrine and epinephrine** from tyrosine in the adrenal medulla and central nervous system.
3. In **tyrosine** degradation at the *p-hydroxyphenylpyruvate* hydroxylase step and at the *homogentisate dioxygenase* step.
4. Ascorbic acid is necessary for the hydroxylation of **tryptophan** to 5-hydroxy tryptophan. This is required for the formation of **serotonin.**
5. Ascorbic acid reduces ferric **iron** to ferrous state, which is preferentially absorbed from the intestine.
6. It is useful for re-conversion of **met-hemoglobin** to hemoglobin.

ASCORBIC ACID

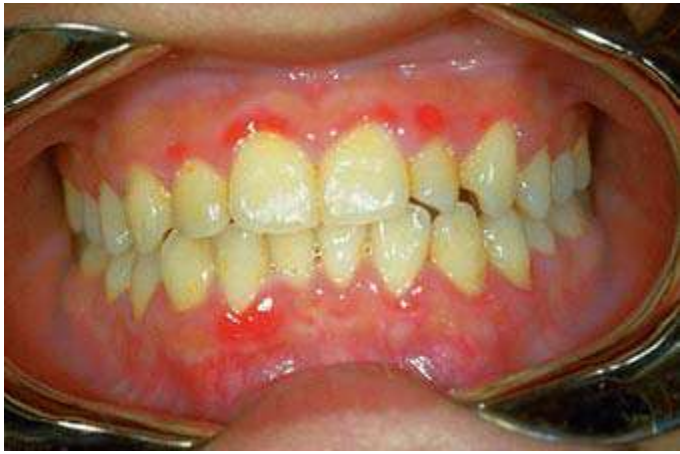
Biochemical Role: as a **coenzyme** in following reactions:

7. Ascorbic acid helps *folate reductase* to reduce folic acid to tetrahydrofolic acid. Thus it helps in the maturation of RBC.
8. Vitamin C helps in the synthesis of bile acids from cholesterol. The initial *7-alphahydroxylase* step is stimulated by the vitamin.
9. Role in adrenal **steroidogenesis.**
10. As an **anti-oxidant** vitamin C reduces risk for cancer & cataract.

- **Sources:** Rich sources are amla, guava, lime, lemon and green leafy vegetables.

- **RDA:** 90mg/d in males
  75mg/d in females

ASCORBIC ACID



- **Deficiecy disorder: Scurvy**
- a disease characterized by sore and spongy gums, loose teeth, fragile blood vessels, swollen joints, and anemia.
- most of the deficiency symptoms can be explained by a deficiency in the hydroxylation of **collagen**, resulting in defective connective tissue.
- The reasons for anemia may be:

a. Loss of blood by hemorrhage

b. Decreased iron absorption

c. Decreased tetrahydrofolic acid

d. Accumulation of met-hemoglobin.

	VITAMIN C
OTHER NAMES	**ASCORBIC ACID**
ACTIVE FORM	L-ascorbic acid and dehydroascorbic acid
FUNCTION	Hydroxylation and reduction reactions required for: Collagen, neurotransmitter, bile acids, steroid synthesis Tyrosine and tryptophan metabolism ferric **iron** to ferrous state, THF formation Antioxidant role
DEFICIENCY	Scurvy

Case-Vitamin C

A nine year old boy was brought to the OPD with bleeding gums, vague bone pains, small red spots on skin and recurrent respiratory infections. History revealed lack of fresh vegetables and fruits in diet.

Lab investigation shows Hb- 8gm/dl.

- What is the probable diagnosis?
- What is the biochemical basis of the findings?
- What are the sources & RDA of this factor?

THE WATER-SOLUBLE VITAMINS

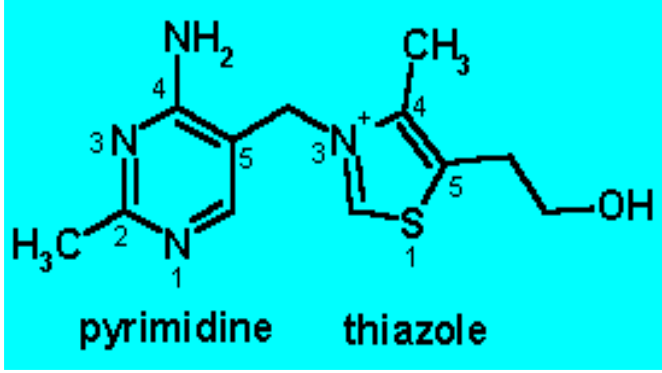
VITAMIN B COMPLEX
AND
VITAMIN C

Vitamin B complex

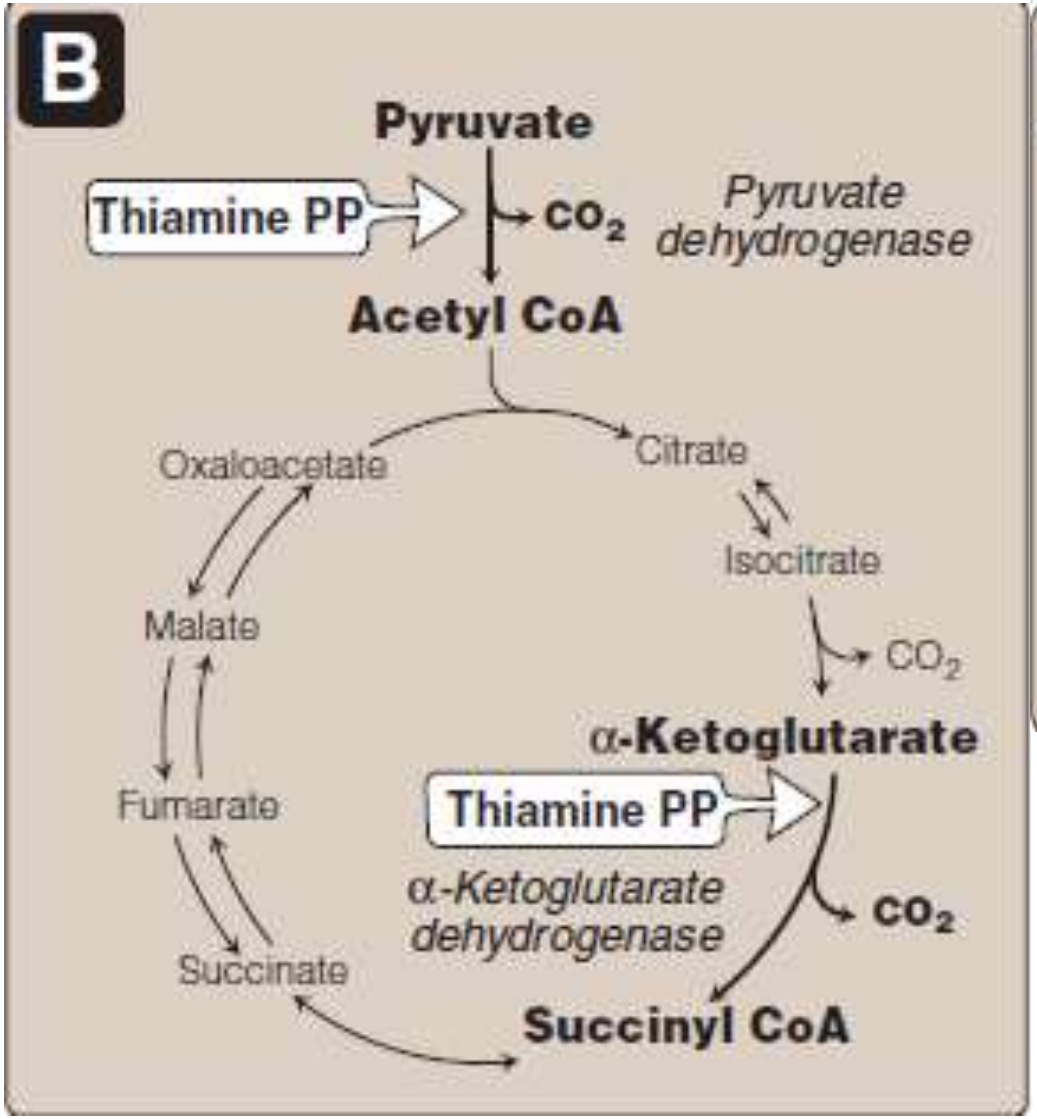
Energy yeilding	Haemato-poietic
Thiamin (B1)-S containing	Folic Acid(B9)
Riboflavin (B2)	Cobalamin (B12)
Niacin(B3)	
Pyridoxine (B6)	
Biotin(B7)-S containing	
Pantothenic acid(B5)-S containing	

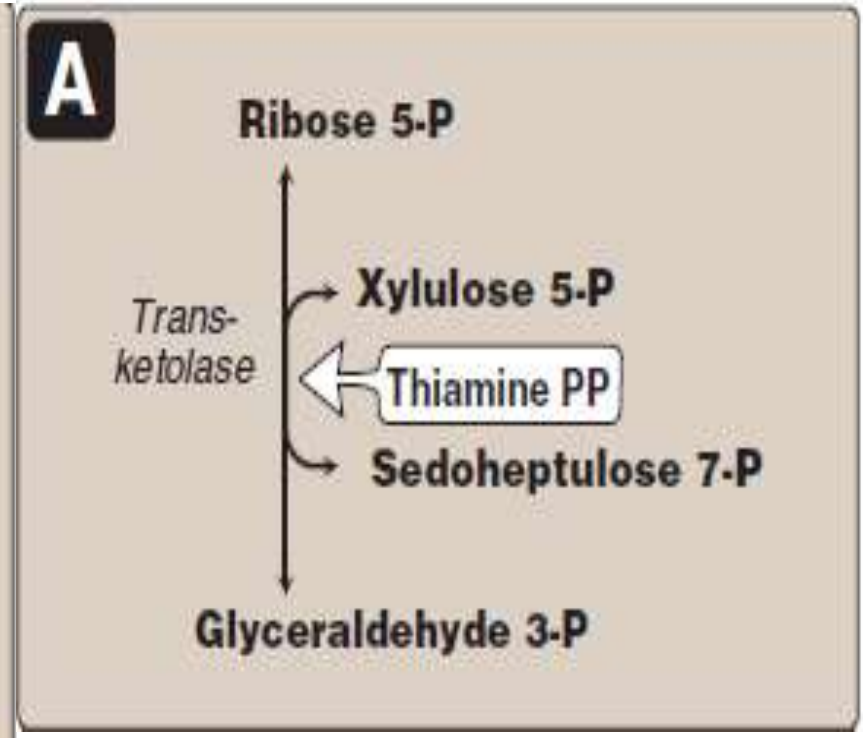
THIAMINE

(Vitamin B1/Aneurin/
Anti-neuritic/Anti-beriberi Factor)



- **Structure:** substituted pyrimidine ring linked to a substituted thiazole ring by a methylene bridge
- **Sulphur-containing vitamin**
- **Active form: Thiamine pyrophosphate(TPP)**
- **Biochemical Role:** Acts as a **co-enzyme** for:
- **Oxidative decarboxylation** of
  - **Pyruvate to Acetyl CoA (PDH)**
  - **α- Ketoglutarate to Succinyl CoA (α- KGDH)**
  - **α-ketoacids of branched chain amino acids**
- **Transfer of keto group in HMP shunt (transketolase)**
- **Acetylcholine synthesis**


B
Pyruvate
Thiamine PP
CO_2
Pyruvate dehydrogenase
Acetyl CoA
Oxaloacetate
Citrate
Isocitrate
Malate
CO_2
α-Ketoglutarate
Fumarate
Thiamine PP
α-Ketoglutarate dehydrogenase
CO_2
Succinate
Succinyl CoA


A
Ribose 5-P
Trans-ketolase
Xylulose 5-P
Thiamine PP
Sedoheptulose 7-P
Glyceraldehyde 3-P

SOURCES:

- Aleurone(outer) layer of cereals (food grains) is a rich source of thiamine. Therefore whole wheat flour and unpolished hand pound rice have better nutritive value than completely polished refined foods.
- Parboiling process of rice retains the vitamin.
- Draining of water in which rice is cooked leads to loss of Thiamine.

RDA:

- It depends on calorie intake (0.5 mg/1000 calories).
- Requirement is 1-1.5 mg/day.

DEFICIENCY DISORDER- BERI-BERI

- **Dry beriberi:** characterized by neuromuscular manifestations like mental depression, peripheral neuropathy, irritability, weakness of muscles and muscle incoordination.
- **Wet beriberi:** characterized by cardiovascular manifestations like edema, palpitation, breathlessness and heart failure.
- **Infantile beriberi:** Signs of infantile beriberi include tachycardia, vomiting, convulsions, and, if not treated, death.
- **Wernicke-Korsakoff syndrome:** Wernicke's encephalopathy with Korsakoff's psychosis, which is associated especially with alcohol and drug abuse. Characterized by apathy, loss of memory, ataxia, and a rhythmic to-and-fro motion of the eyeballs (nystagmus).

RIBOFLAVIN

(B2/Lactoflavin)

Structure:

dimethyl isoalloxazine ring to which a ribitol is attached.

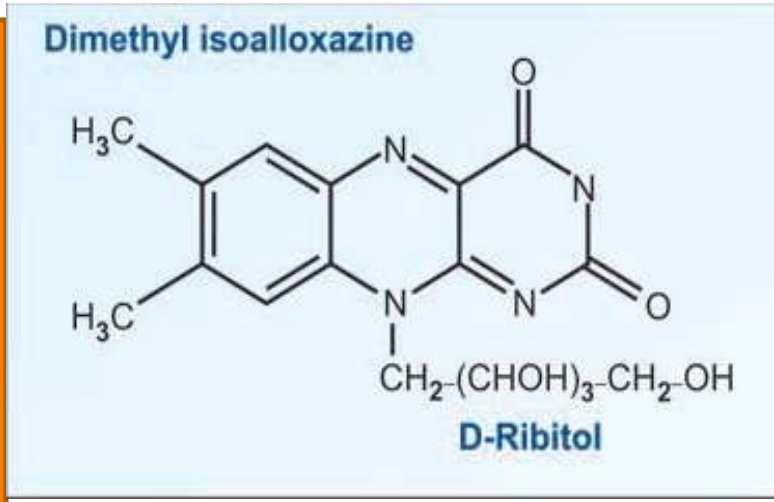
Active form:

FMN

FAD

Biochemical Role:

- FMN and FAD are each capable of reversibly accepting two hydrogen atoms, forming FMNH2 or FADH2.
- FMN and FAD are bound tightly to flavoenzymes that catalyze the oxidation or reduction of a substrate



FMN-dependent Enzymes:

1. L-amino acid oxidase
2. Complex I of ETC (NADH dehydrogenase)

FAD-dependent Enzymes:

1. acyl CoA dehydrogenase (Acyl CoA ⟶ unsaturated acyl CoA)
2. xanthine oxidase (Xanthine ⟶ uric acid)
3. pyruvate dehydrogenase (Pyruvate ⟶ acetyl CoA)
4. α-ketoglutarate dehydrogenase(α-ketoglutarate → succinyl CoA)
5. Complex II of ETC (succinate dehydrogenase)
6. Glycerol 3-P DH (Glycerol 3-P ⟶ DHAP)

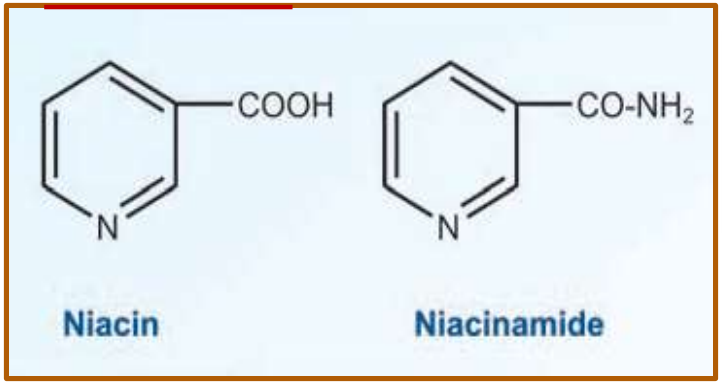
- **Deficiency Manifestations:**
- Dermatitis (inflammation of the skin),
- cheilosis (inflammation of the lips),
- Angular stomatitis(fissuring at the corners of the mouth),
- glossitis (the tongue appearing smooth and purplish)
- Photophobia
- **Sources:** milk, meat, eggs and cereals
- **RDA:** 1-1.5 mg/day

VITAMIN	THIAMIN	RIBOFLAVIN
OTHER NAMES	**(**B1/Aneurin/Anti-neuritic/Anti-beriberi Factor)	(B2/Lactoflavin)
ACTIVE FORM	**Thiamine pyrophosphate(TPP)**	**FMN, FAD**
FUNCTION	Coenzyme of enzymes catalyzing: Pyruvate → acetyl CoA α-Ketoglutarate → Succinyl CoA Ribose 5-P + xylulose 5-P → Sedoheptulose 7-P + Glyceraldehyde 3-P Branched-chain amino acid oxidation	Ox-Red reactions
DEFICIENCY	Beriberi Wernicke-Korsakoff syndrome (most common in alcoholics)	Dermatitis, Cheilosis Angular stomatitis, glossitis Photophobia

NIACIN

(B3/Pellagra Preventive Factor/Nicotinic Acid)

Structure



Niacin-monocarboxylic derivative of pyridine
niacinamide/nicotinamide-amide derivative

Co-enzyme/Active form: NAD & NADP

Biochemical Role:

In Dehydrogenase reactions

Eg; pyruvate DH, α-ketoglutarate DH

NAD^+ ⇕ Glutamate DH

$NADP^+$ ⇕ Eg; G6PD, Malic enz.

Reduced form

$NADH + H^+$ → ETC

$NADPH + H^+$ → Reductive syntheses

NIACIN

Biosynthesis: 60mg of Tryptophan $\xrightarrow{\text{PLP}}$ 1mg of niacin

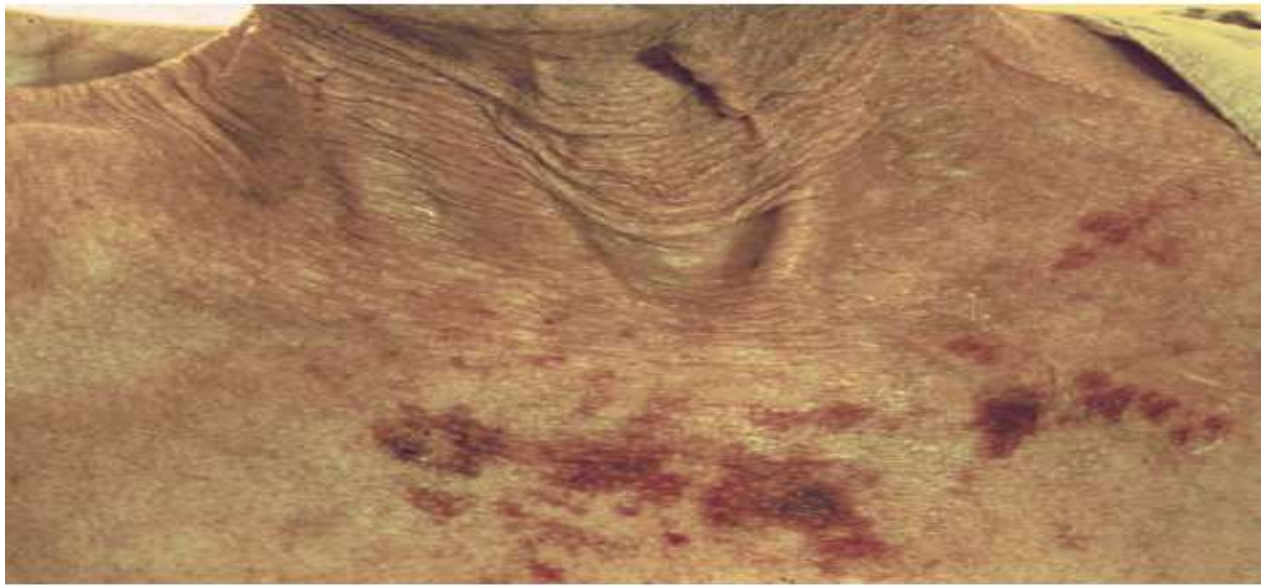
RDA: 14mg/d in females
16mg/d in males

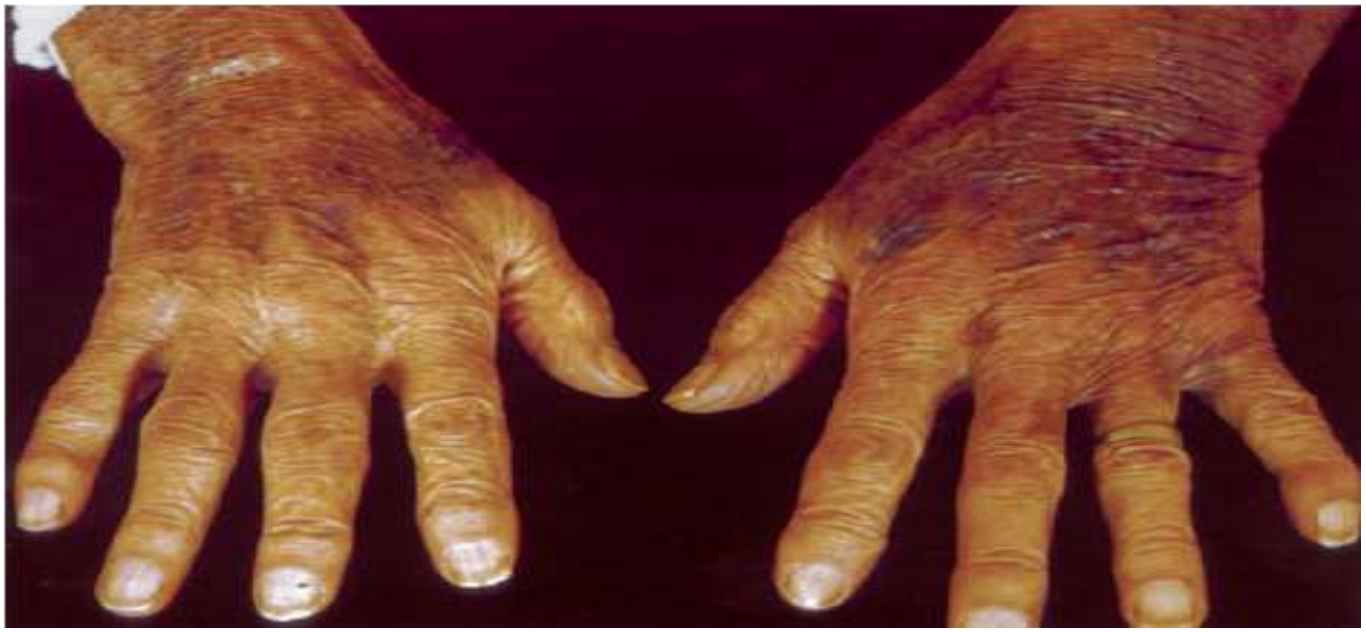
Sources: meats, nuts, legumes and cereals. Corn/Maize and Jowar are deficient in niacin and tryptophan.

Deficiency disorder: **Pellagra** characterized by 3 Ds:

- Dermatitis- b/l symmetrical, exposed areas, Casal's necklace
- Diarrhoea
- Dementia/depression $\longrightarrow$ DEATH

Causes: tryptophan deficiency in diet, Hartnup's disease, Carcinoid syndrome, INH therapy, PLP deficiency

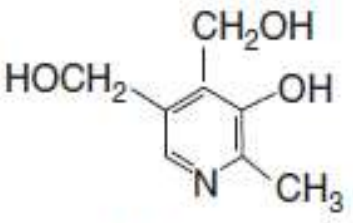




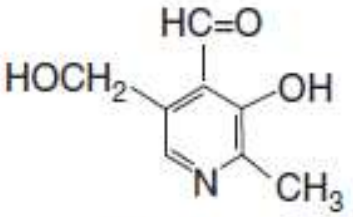
Therapeutic Use of Niacin

- Nicotinic acid inhibits the flux of free fatty acids from adipose tissue; so acetyl CoA pool is reduced; and hence serum **cholesterol is lowered.**
- The liver normally uses these circulating fatty acids as a major precursor for triacylglycerol synthesis.Thus, niacin causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production.
- LDL is derived from VLDL in the plasma. Thus, both **plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered.**

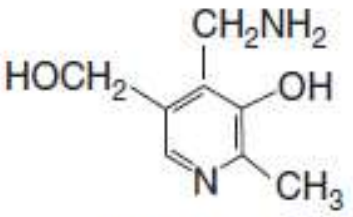
PYRIDOXINE
(VITAMIN B6)



Pyridoxine



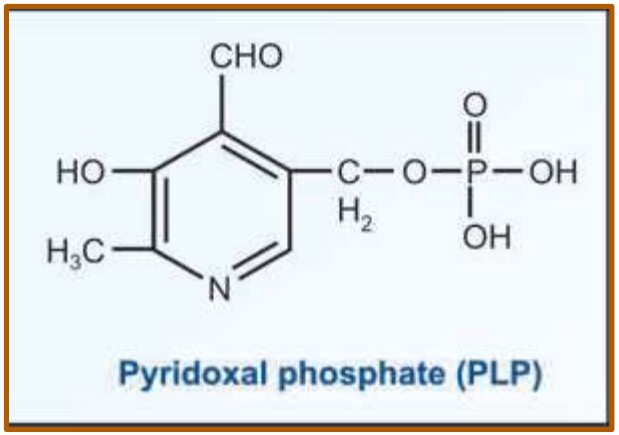
Pyridoxal



Pyridoxamine

Structure: family of 3 related pyridine derivatives;

Co-enzyme/Active form: **pyridoxal phosphate (PLP)**



Pyridoxal phosphate (PLP)

PYRIDOXINE

Biochemical Role:

Pyridoxal phosphate is a coenzyme for many enzymes involved in amino acid metabolism:

Reaction type	Example
Transamination	Oxaloacetate + glutamate ⟶ aspartate + α-ketoglutarate
Deamination	Serine → pyruvate + NH3
Decarboxylation	Histidine → histamine + CO2
Condensation	Glycine + succinyl CoA → δ-aminolevulinic acid (Heme synthesis)

PYRIDOXINE

Biochemical Role:

- Coenzyme for glycogen phosphorylase
- required for the synthesis of niacin from tryptophan (**one vitamin is necessary for synthesis of another vitamin)**
- PLP is involved in the synthesis of sphingolipids and formation of myelin.

RDA: **2mg/d**

SOURCES: meat, fish, egg, milk, vegetables, cereals

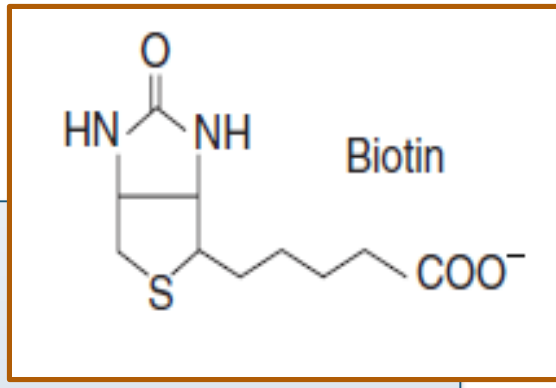
Deficiency Manifestations of Pyridoxine

- **Neurological:** irritability, confusion, depression, peripheral neuropathy due to decreased formation of serotonin, epinephrine, noradrenaline and gamma amino butyric acid (GABA) and sphingolipids.
- **Dermatological:** PLP deficiency in turn leads to niacin deficiency which is manifested as **pellagra.**
- **Hematological:** anaemia (microcytic hypochromic) due to decreased haem synthesis.
- **Isonicotinic acid hydrazide (INH/isoniazid),** an antituberculosis drug can induce deficiency of PLP. Pyridoxine supplementation is, thus, an adjunct to isoniazid treatment.

VITAMIN	NIACIN	PYRIDOXINE
OTHER NAMES	(B3/Pellagra Preventive Factor/Nicotinic Acid)	B6
ACTIVE FORM	**NAD & NADP**	**Pyridoxal Phosphate (PLP)**
FUNCTION	Ox-Red reactions	Amino acid metabolism
DEFICIENCY	Pellagra	Neuropathy Dematitis Anaemia

BIOTIN

B7/Anti-egg white injury factor



Structure: **imidazole** ring fused with a **thiophene** ring with a **valeric acid** side chain

Biochemical Role:

- Biotin acts as co-enzyme for **α-carboxylation reactions.**
- Biotin is covalently bound to the ε-amino groups of lysine residues in biotin-dependent enzymes:
- ***acetyl carboxylase(acetyl CoA ⟶ malonyl CoA)***
- ***propionyl carboxylase(propionyl CoA ⟶ methylmalonyl CoA)***
- ***pyruvate carboxylase(pyruvate ⟶ oxaloacetate)***
- ***methylcrotonyl carboxylase(valine metabolism)***

BIOTIN

- **Biotin deficiency:** **rare** because the vitamin is widely distributed in food. Also, a large percentage of the biotin requirement in humans is supplied by **intestinal bacteria**.
- Deficiency is unknown except among people maintained for many months on **parenteral nutrition** and a very small number who eat abnormally large amounts of **uncooked egg white,** which contains **avidin**, a protein that binds biotin and renders it unavailable for absorption.
- **Deficiency manifestations :** dermatitis, glossitis, loss of appetite, and nausea.
- **Sources:** Liver, yeast, peanut, soya bean, milk and egg yolk.
- About **200-300 mg** will meet the daily requirements.

PANTOTHENIC ACID

Structure: **Pantoic acid** and **β-alanine** in an amide linkage.

Coenzyme form: **CoA**

Biochemical role: ***Acetyl CoA, Propionyl CoA,Succinyl CoA, HMG CoA, Acyl CoA***

Component of ***fatty acid synthase*** complex

Sources: It is widely distributed in plants and animals.It is synthesized by the normal bacterial flora in intestines. Therefore, deficiency is very rare.

Yeast, liver and eggs are good sources.

Requirement: 10mg/d

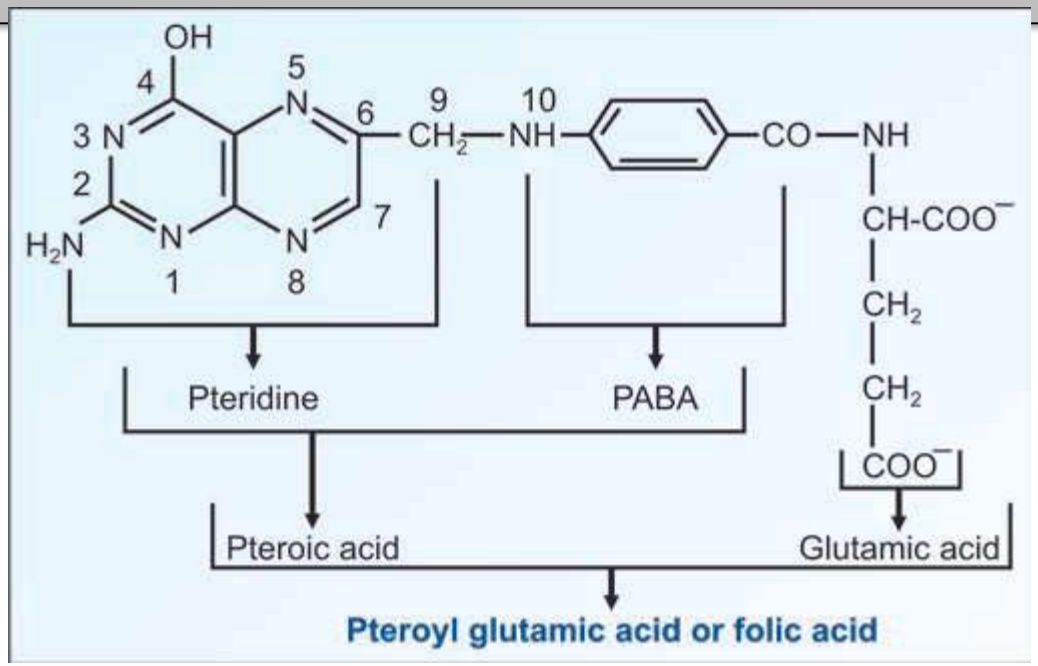
PANTOTHENIC ACID

- **Deficiency manifestation:**
- Gopalan's **Burning Foot Syndrome is manifested** as paresthesia (burning, lightning pain) in lower extremities, staggering gait due to impaired coordination and sleep disturbances.

VITAMIN	BIOTIN	PANTOTHENIC ACID
OTHER NAMES	B7/Anti-egg white injury factor	B5
ACTIVE FORM		CoA
FUNCTION	**α-carboxylation reactions.** *acetyl carboxylase* *propionyl carboxylase* *pyruvate carboxylase* *methylcrotonyl carboxylase*	*acetyl CoA, propionyl CoA, succinyl CoA, HMG CoA, acyl CoA* ***fatty acid synthase***
DEFICIENCY	dermatitis, glossitis, loss of appetite, and nausea.	Gopalan's **Burning Foot Syndrome**

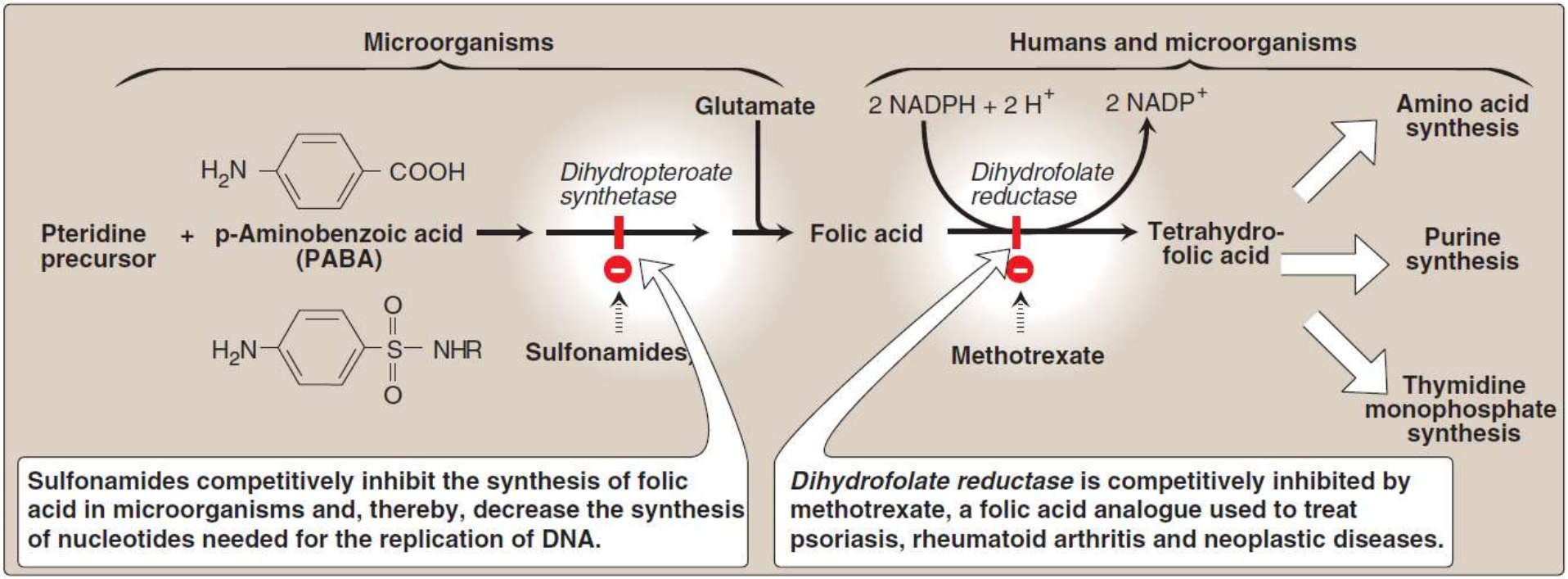
FOLIC ACID
FOLATE/FOLACIN/B9

- The Latin word *folium* means leaf of vegetable.
- Folic acid is abundant in vegetables.
- **Structure:** Pteroyl glutamic acid or folic acid is composed of three constituents: **pteridine** group linked with **para amino benzoic acid (PABA)** attached to **glutamic acid.**



FOLIC ACID

- **Coenzyme form: Tetra hydro folate (THF/H_4folate)**
- Inhibitors of folate metabolism provide cancer chemotherapy & antibacterial & antimalarial drugs.



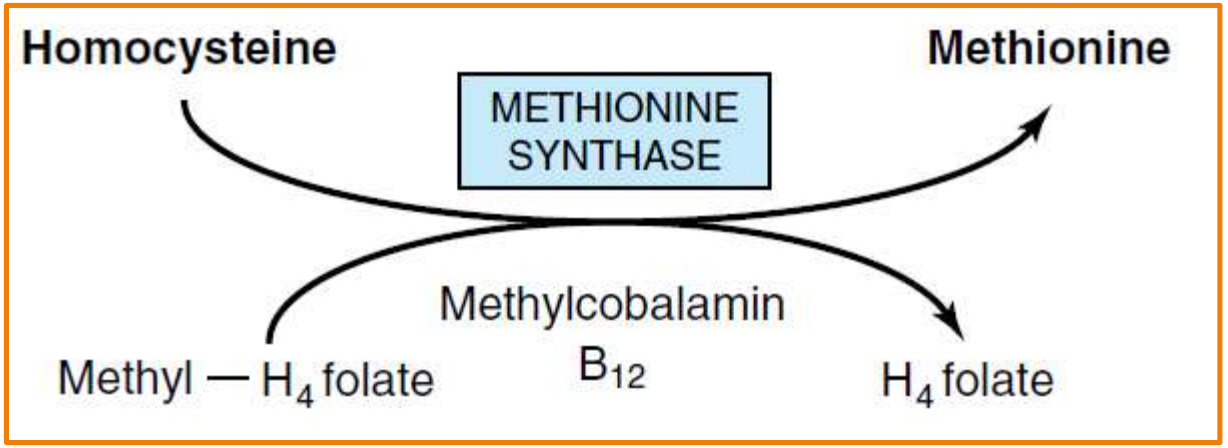
FOLIC ACID

- **Biochemical role:**
- Tetra hydro folate receives one-carbon fragments from donors such as serine, glycine, and histidine and transfers them to intermediates in the synthesis of amino acids, purines, and thymidine mono phosphate (TMP)—a pyrimidine found in DNA.

FOLIC ACID DEFICIENCY

- A primary result of folic acid deficiency is **megaloblastic anemia** caused by diminished synthesis of purines and TMP, which leads to an inability of cells (including red cell precursors) to make DNA and, therefore, they cannot divide.
- Folic acid supplementation before conception and during the first trimester has been shown to significantly reduce the **neural tube defects**.
- Therefore, all women of childbearing age are advised to consume 0.4 mg/day of folic acid to reduce the risk of having a pregnancy affected by neural tube defects.

The Folate Trap



- Vitamin B12 deficiency leads to inhibition of **methionine synthase** activity causing **homocysteinuria/hyperhomocyteinemia** and the **trapping** of folate as methyltetrahydrofolate.

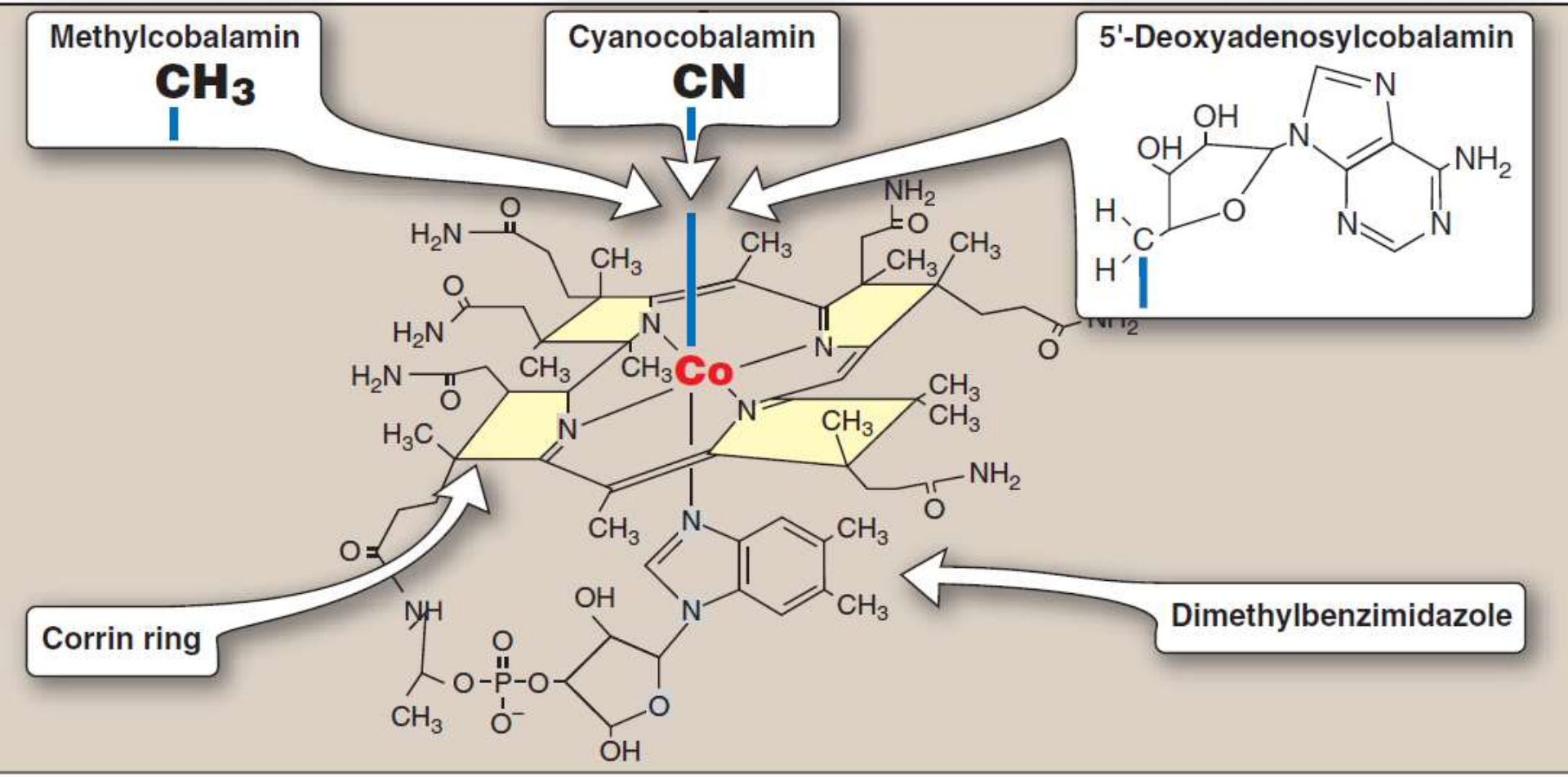
- There is therefore functional deficiency of folate secondary to the deficiency of vitamin B12 which leads to **megaloblastic anaemia**.

- Elevated blood homocysteine is an associated risk factor for **atherosclerosis, thrombosis, and hypertension.**

COBALAMIN

(B12/Extrinsic Factor Of Castle/Antipernicious Anemia Factor)

Structure



- Intrinsic factor is secreted by the gastric parietal cells.
- Vitamin B12 is absorbed from the distal third of the ileum via receptors that bind the intrinsic factor-vitamin B12 complex but not free intrinsic factor or free vitamin.
- **Transcobalamin, a glycoprotein,** is the specific transport protein.
- It is stored in the liver cells, as **ado-B12 form,** in combination with **transcorrin.**
- In the blood, **methyl B12 form** is predominant.

Sources:

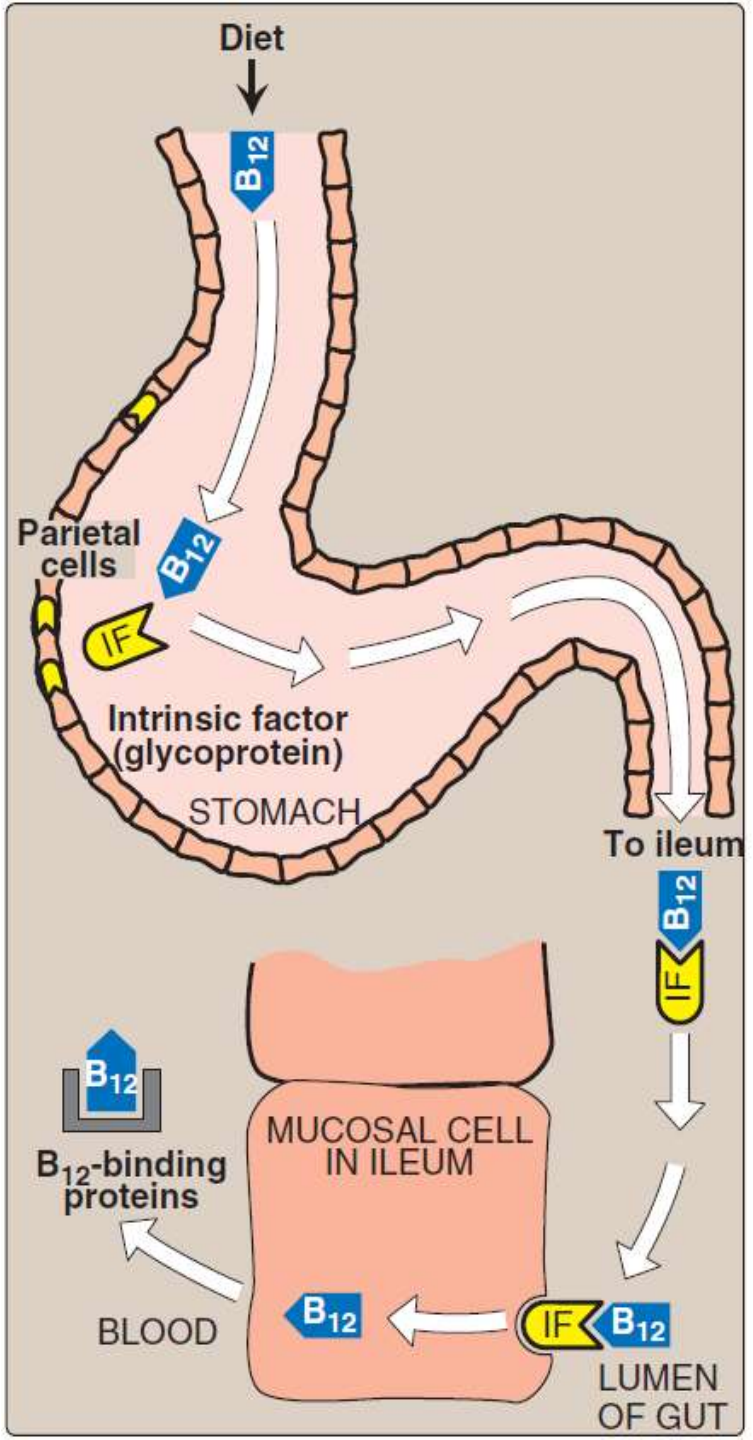
not present in vegetables.

Liver is the richest source.

Curd is a good source, because lactobacillus can synthesize B12

Synthesized by intestinal bacteria.

RDA: 2µg/d

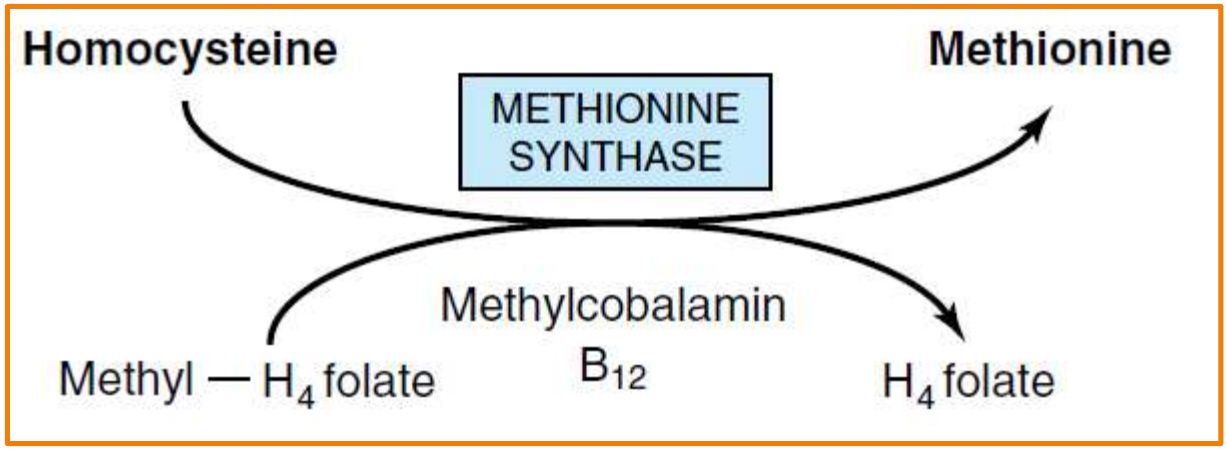


COBALAMIN

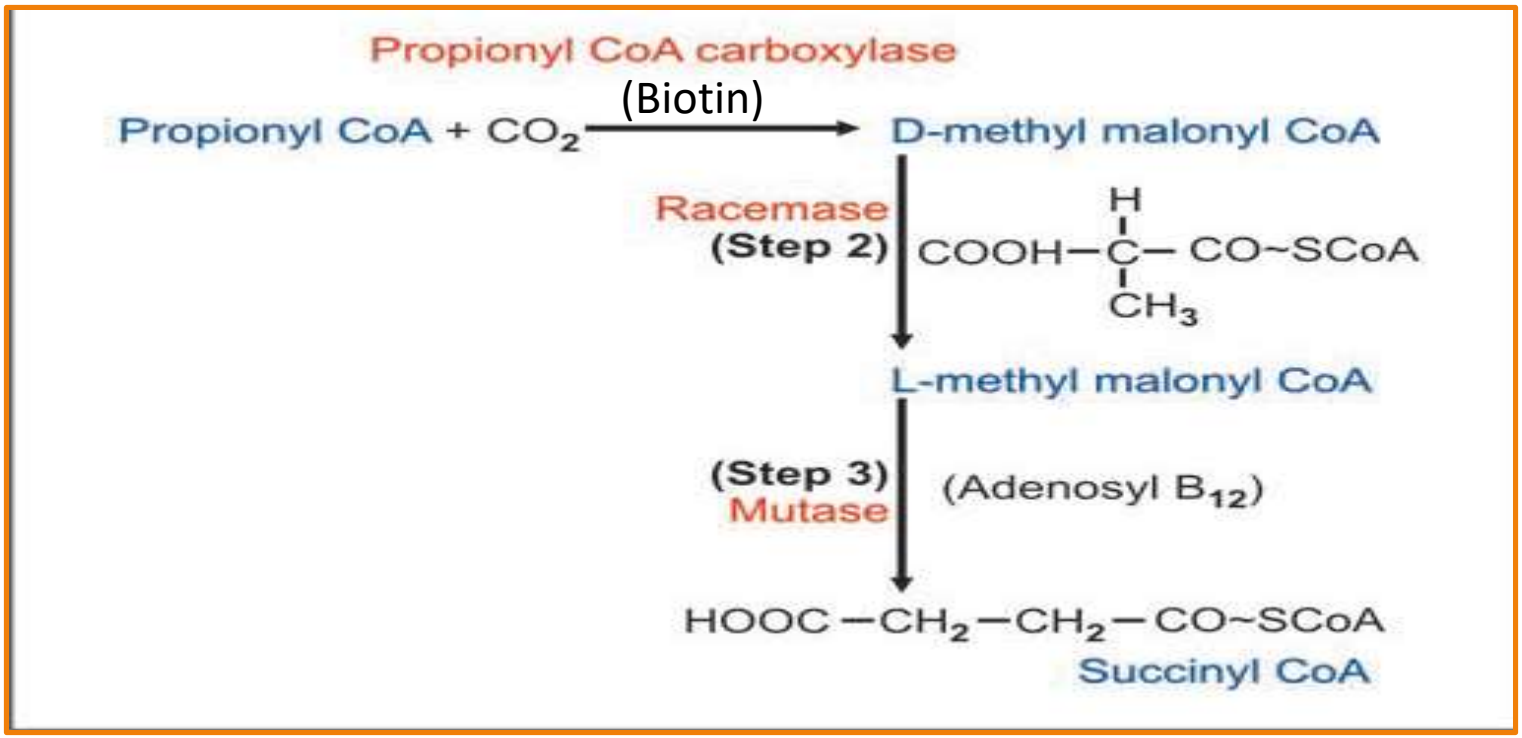
Coenzyme form: **methylcobalamin and**

5'-deoxyadenosylcobalamin(Ado-B12)

Biochemical role:



Biochemical role of 5'-deoxyadenosylcobalamin



In B12 deficiency, methyl malonyl CoA is excreted in urine (**methyl malonic aciduria).**

Causes of B12 Deficiency

1. **Nutritional**

   very common in India, among vegetarians of low socioeconomic group. The only source for B12 in vegetarian diet is curd / milk, and lower income group may not be able to afford it.

2. **Decrease in absorption**

   Absorptive surface is reduced by gastrectomy, resection of ileum and malabsorption syndromes.

3. **Addisonian pernicious anemia**

   The commonest cause of pernicious anemia is failure of the absorption of vitamin B12 rather than dietary deficiency.

   This can be due to failure of intrinsic factor secretion caused by

   - autoimmune disease of parietal cells or
   - to generation of anti-intrinsic factor antibodies.

COBALAMIN

- **Deficiency Manifestations:**
- **Folate trap** ⟶ megaloblastic anaemia
- ⟶ hyperhomocyteinemia & homocysteinuria
- **Neurological manifestations:**
- Demyelination of nerves due to the non-availability of active methionine.
- Therefore methylation of phosphatidyl ethanolamine to phosphatidyl choline is not adequate.
- There is demyelination affecting cerebral cortex as well as dorsal column and pyramidal tract of spinal cord (**Subacute combined degeneration)**
- Accumulation of methyl malonyl CoA ⟶ **methyl malonic aciduria**

VITAMIN	FOLIC ACID	COBALAMIN
OTHER NAMES	**Folate/Folacin/B9**	**(B12/Extrinsic Factor Of Castle/Antipernicious Anemia Factor)**
ACTIVE FORM	**Tetra hydro folate (THF/H_4folate)**	**Methylcobalamin 5'-deoxyadenosylcobalamin (Ado-B12)**
FUNCTION	receives one-carbon fragments from donors and transfers them to intermediates in the synthesis of amino acids, purines, and pyrimidines.	Homocysteine ⟶ Methionine Propionyl CoA ⟶ Succinyl CoA
DEFICIENCY	megaloblastic anemia neural tube defects.	**Folate trap** l.t. megaloblastic anaemia,hyperhomocyteinemia & homocysteinuria **Neurological manifestations: (Subacute combined degeneration)** **methyl malonic aciduria**

Case-Thiamin

A 40 years old male patients complained of muscular weakness, pain & numbness of legs, indigestion, constipation and lack of appetite. On Examination patient had tachycardia, enlarged heart, peripheral edema and neuropathy. History revealed that polished rice is his staple diet.

- What is the probable diagnosis?
- What are sources and RDA for this factor.
- Give active form and two biochemical reactions requiring it.

Case-Niacin

A 10 yr agricultural labourer living in a remote village in central India was on a maize and jowar staple diet for several years. He developed a rash on those parts of the body exposed to sunlight, chronic diarrhea and associated psychiatric symptoms such a delirium and loss of memory.

- What is the diagnosis? This case is related to which deficiency?
- What are the coenzyme forms of this vitamin?
- Give the RDA and biochemical functions of this vitamin.

Case-Cobalamin

A strict vegetarian female was anemic and had complaints of weakness, numbness and tingling of fingers. Lab investigations show elevated levels of methyl malonic acid in urine and Hb-8 gm/dl.

- What is the probable diagnosis?
- What is the biochemical basis of the findings?
- What are the sources & RDA of this factor?