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Vitamins

Modified by: Nermeen Abuhalaweh

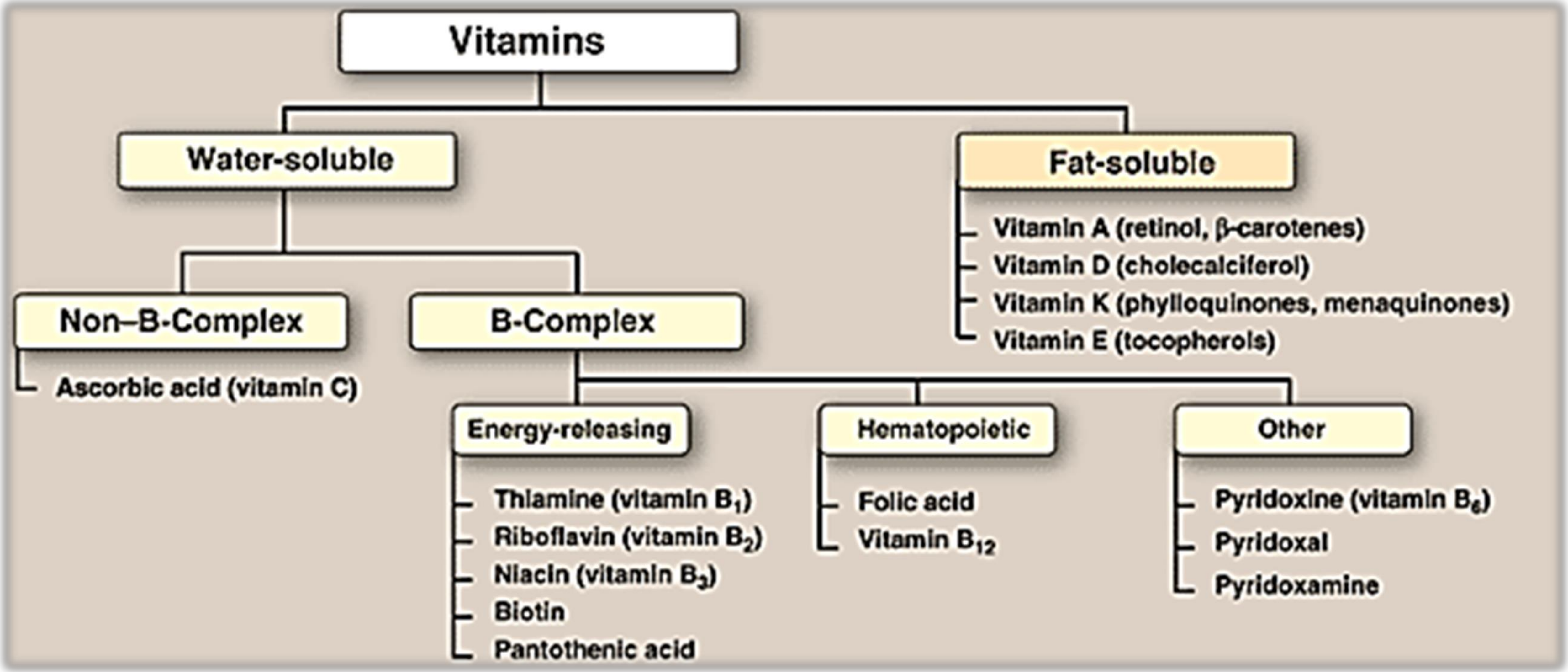
Vitamins

- Organic compounds required by an organism in tiny amounts as a vital nutrient
  As they function in helping enzymes, which are also found in tiny amounts.
- Cannot be synthesized in sufficient quantities, & must be obtained from diet
  by our cells, but maybe produced by microbiota INSIDE our bodies.
- The term is conditional both on the circumstances & on the particular organism (ascorbic acid, humans, other animals) (vitamin D, human diet)
  Vitamin C
- Thirteen vitamins are universally recognized at present
  - 4 lipid-soluble
  - 9 water-soluble

Vitamins

- Vitamins have diverse biochemical functions:
  - Hormone-like functions (regulators): regulators of mineral metabolism (e.g., vitamin D), or regulators of cell & tissue growth & differentiation (e.g., vitamin A)
  - Anti-oxidants (e.g., vitamins E & C)
  - Precursors for enzyme cofactors (vitamin B subclasses)

Classification



FOLIC ACID (VITAMIN B9) – Folate

- Plays a key role in one-carbon metabolism

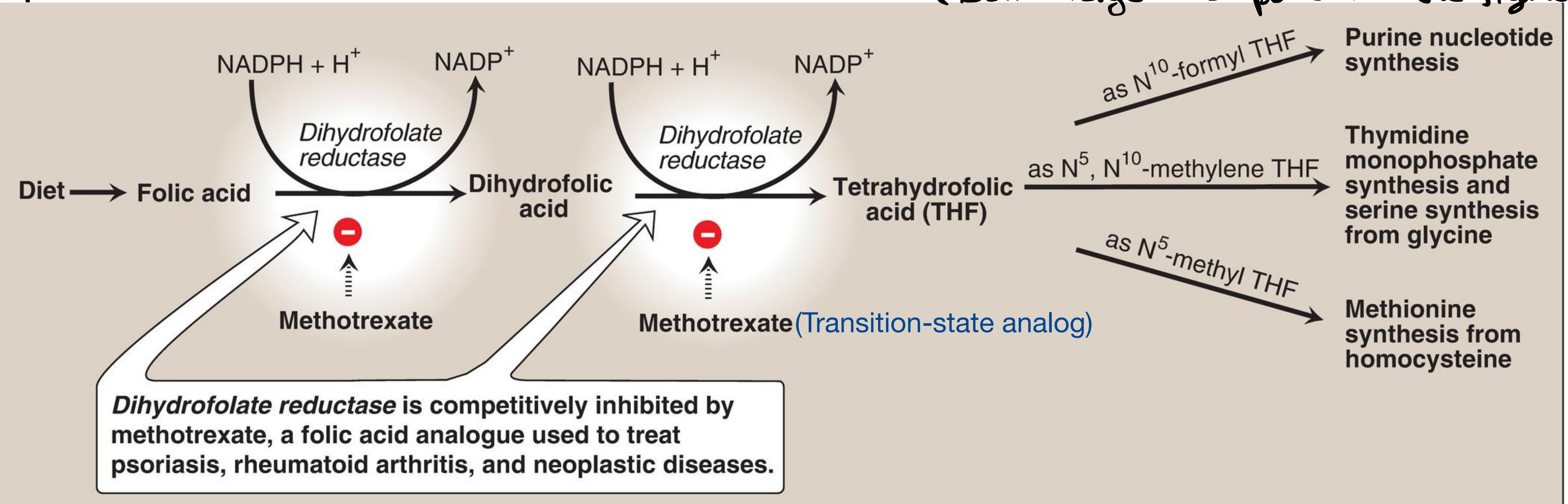
- Folic acid deficiency is probably the most common vitamin deficiency, particularly among pregnant women and individuals with alcoholism

- Leafy, dark green vegetables are a good source of folic acid

Function

- Tetrahydrofolate (THF), the reduced, coenzyme form of folate (Gained electrons).
- Receives one-carbon fragments from donors as serine, glycine, and histidine
- Transfers them to intermediates in the synthesis of amino acids, purine nucleotides, and thymidine monophosphate (TMP), a pyrimidine nucleotide incorporated into DNA.

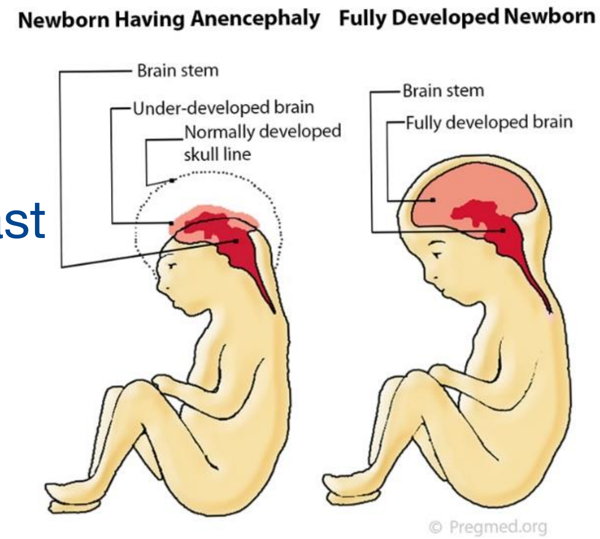
(Don't forget to ponder the figure)



Folate and anemia

- Causes of deficiency:
  - Increased demand (pregnancy and lactation)
  - Poor absorption (pathology or alcoholism)
  - Drugs (methotrexate)
  - Folate-free diet (few weeks)

  -May result from the increased demand on fast food.



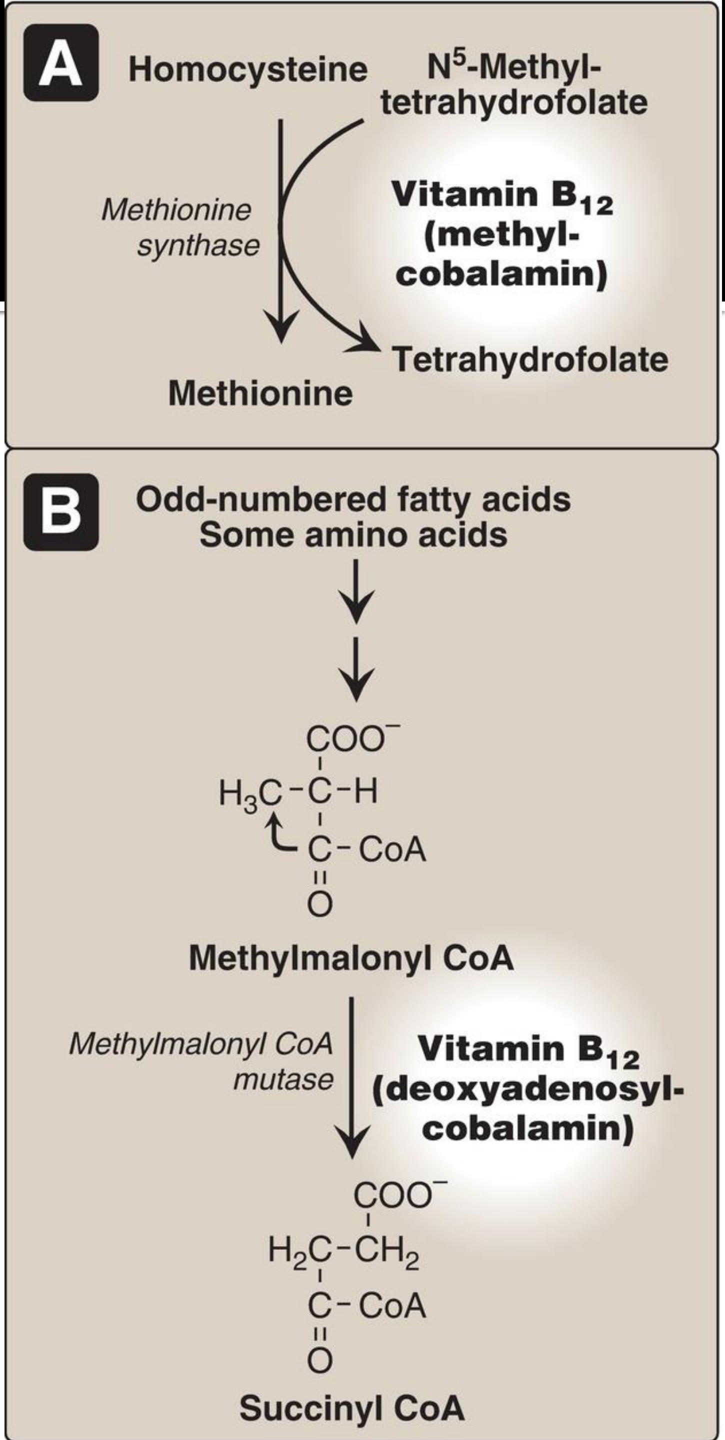
- Might result in:
  - Neural tube defects (NTD): Spina bifida and anencephaly
  - affect ~3,000 pregnancies in the US annually

Accordingly

- Folic acid supplementation before conception and during the first trimester
- All women of childbearing age (400 µg/day) of folic acid to reduce the risk, 10 times if a previous pregnancy was affected
- In the U.S., addition of folic acid to wheat flour and enriched grain products, resulting in a dietary supplementation of ~0.1 mg/day
- This supplementation allows ~50% of all reproductive-aged women to receive 0.4 mg of folate from all sources

COBALAMIN (VITAMIN B12)

- Required for two essential enzymatic reactions
  - Remethylation of homocysteine (Hcy) to methionine
  - Isomerization of methylmalonyl coenzyme A (CoA), which is produced during the degradation of some amino acids (isoleucine, valine, threonine, and methionine) and fatty acids (FA) with odd numbers of carbon atoms

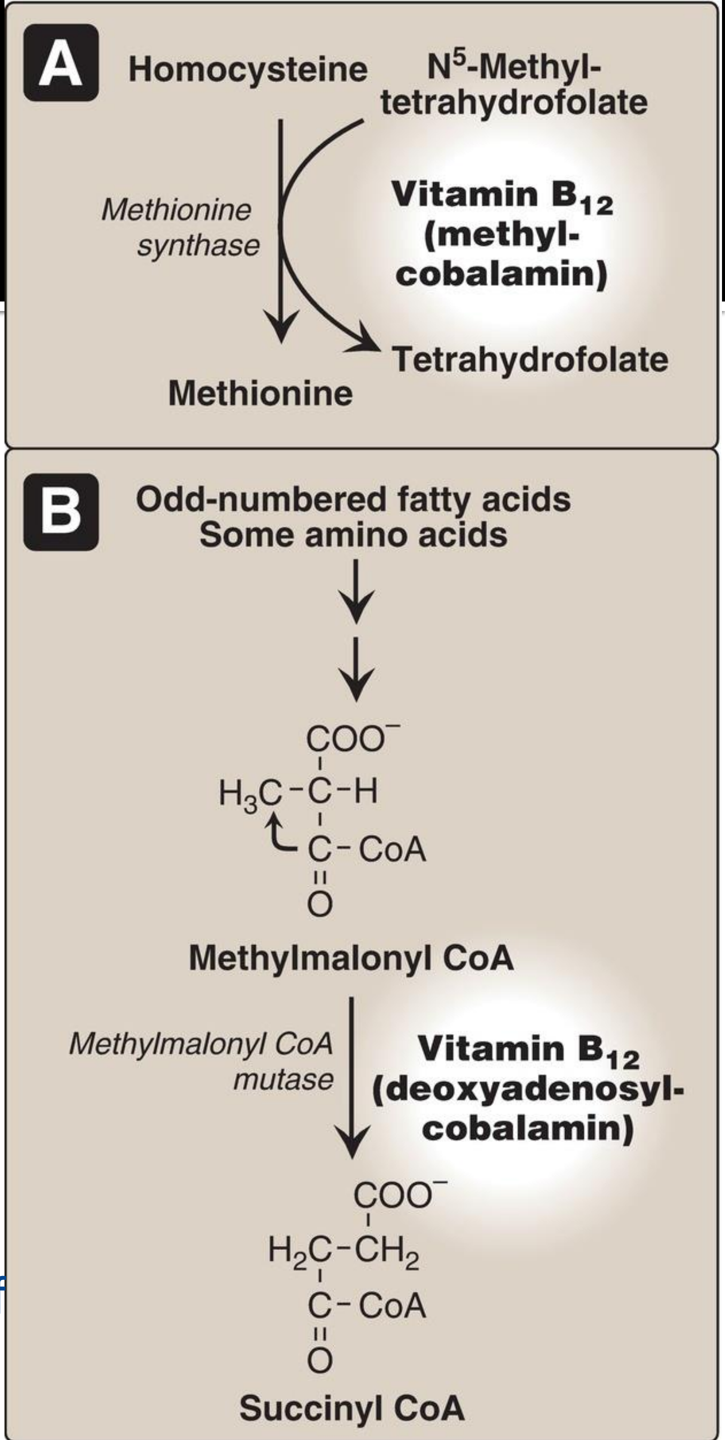


COBALAMIN (VITAMIN B12)

- When cobalamin is deficient, unusual (branched) FA accumulate and become incorporated into cell membranes, including those of the central nervous system (CNS)

- This may account for some of the neurologic manifestations of vitamin B12 deficiency

- Folic acid (as N5-methyl THF) is also required in the remethylation of Hcy. Therefore, deficiency of B12 or folate results in elevated Hcy levels Results in increased risks of cardiovascular diseases.

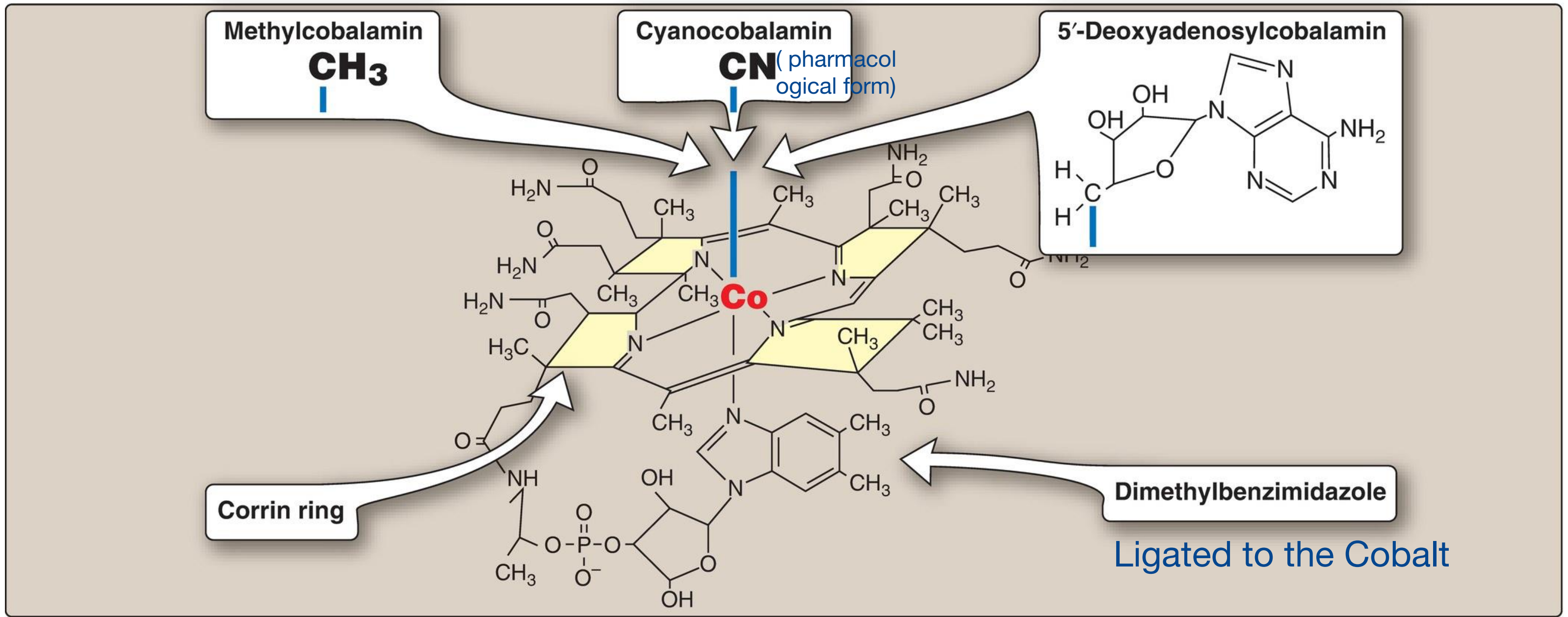


Structure and coenzyme forms

- A "corrin" ring system vs. Porphyrin (Cobalt)
- The remaining coordination: nitrogen of 5,6-dimethylbenzimidazole and with cyanide in commercial preparations (cyanocobalamin)
- The physiologic coenzyme are:
  - 5′-deoxyadenosylcobalamin
  - Methylcobalamin

-Vinyl connects each two pyrrole rings.

B12 is synthesized in microorganisms, methylcobalamin and deoxyadenosylcobalamin are found in the normal forms, while cyanocobalamin is found in the pharmacological form.

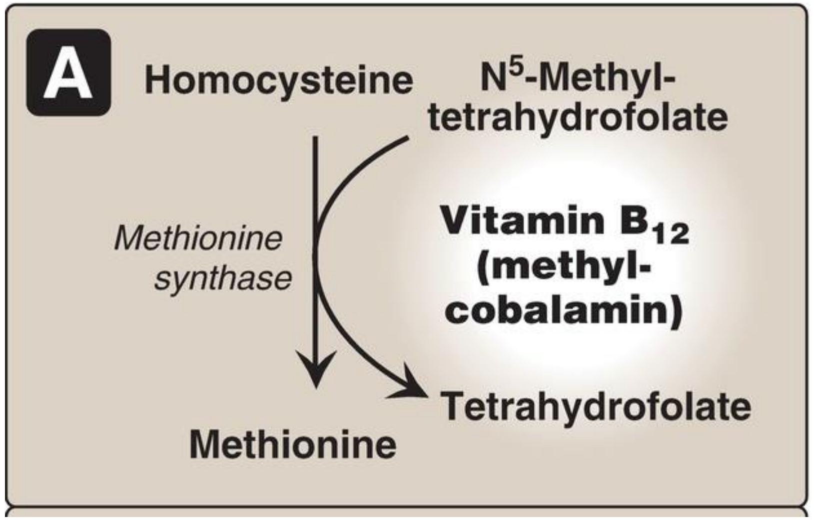


Distribution

- Vitamin B12 is synthesized only by microorganisms, and it is not present in plants
- Animals obtain the vitamin preformed from their intestinal microbiota or by eating foods derived from other animals
- Cobalamin is present in appreciable amounts in liver, red meat, fish, eggs, dairy products, and fortified cereals

Folate trap hypothesis

- Effects of cobalamin deficiency are most pronounced in rapidly dividing cells, such as the erythropoietic tissue of bone marrow and the mucosal cells of the intestine
- Such tissues need both the N5,N10-methylene and N10-formyl forms of THF for the synthesis of nucleotides required for DNA replication
- However, in vitamin B12 deficiency, the utilization of the N5-methyl form of THF is impaired - accumulates
- Deficiency of THF forms needed in purine and TMP synthesis, resulting in megaloblastic anemia(Release of large erythrocytes)

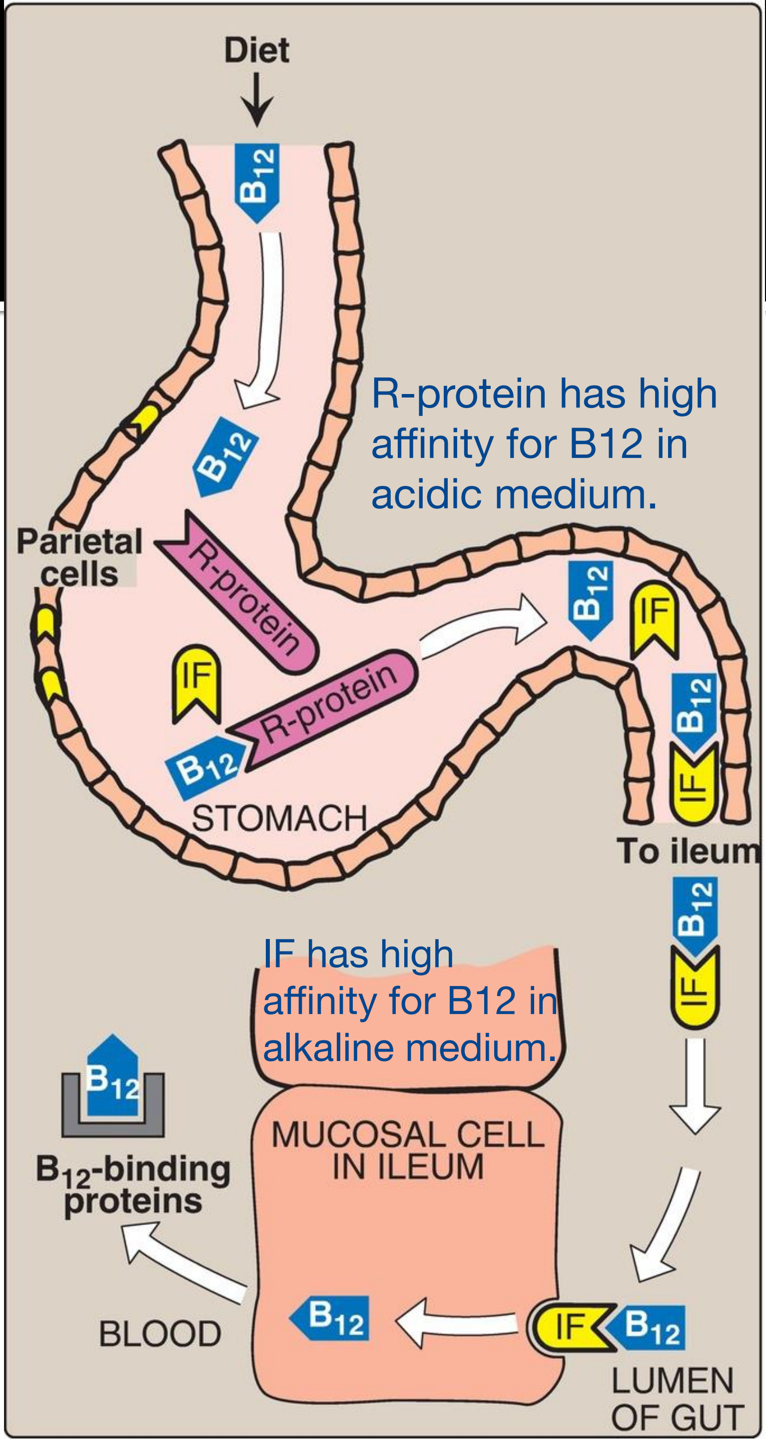


Clinical indications for cobalamin

- In contrast to WS vitamins, significant amounts (2–5 mg) of vitamin B12 are stored in the body
- May take several years for clinical symptoms to develop
- Deficiency happens much more quickly (in months) if absorption is impaired

Pernicious anemia

- Severe malabsorption of vitamin B12 leads to pernicious anemia
- Most commonly a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of IF (Intrinsic factor)
- Impaired absorption
- Intestine → complexed to intrinsic factor (IF, a glycoprotein) → cubilin (receptor) → circulation (transcobalamin)
- Malabsorption in the elderly (achlorhydria)
- Individuals with cobalamin deficiency are usually anemic (folate recycling is impaired)



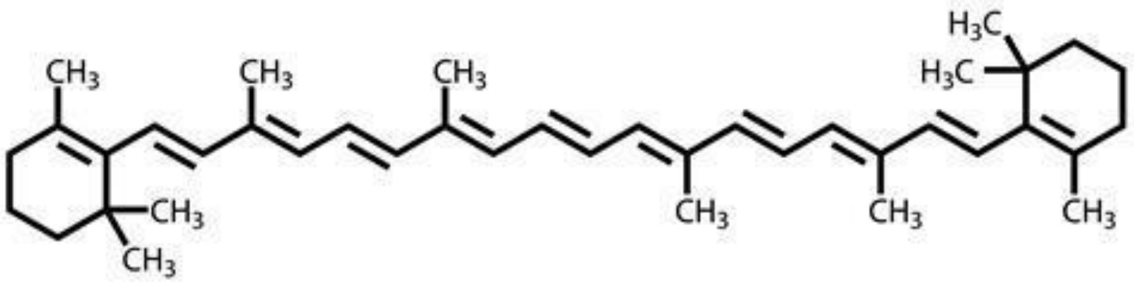
Fat soluble vitamins

No one specific structure, instead a group of related molecules (of each type).

Vitamin	Main function	Deficiency
A	Roles in vision, growth, reproduction	Night blindness, cornea damage
D	Regulation of Ca^{+2} & phosphate metabolism	Rickets (children), Osteomalacia (adults)
E	Antioxidant	RBCs fragility
K	Blood coagulation	Subdermal hemorrhaging

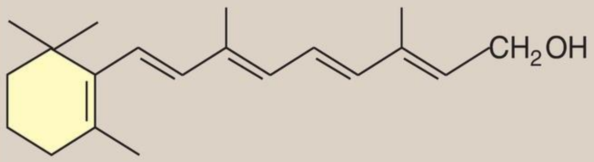
All fat-soluble vitamins are groups and carried in chylomicrons

Vitamin A

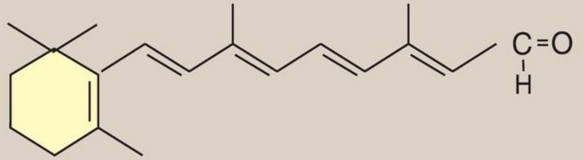


- ✓ The retinoids, a family of molecules essential for vision, growth, reproduction, & maintenance of epithelial tissues
- ✓ Retinal and retinol are inter-convertible (Though they perform similar functions "interconvertible")
- ✓ β-Carotene: oxidatively cleaved in the intestines to yield 2 molecules of retinal (An aldehyde that can be either reduced to alcohol (retinol) or oxidized to carboxylic acid (retinoic acid)).
- ✓ Retinoic acid, mediates most of the actions of the retinoids, except for vision and spermatogenesis

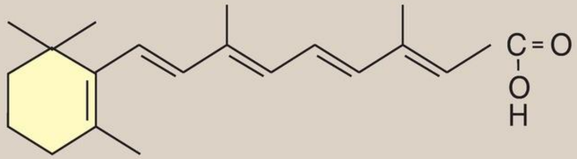
Oxidation of retinal is irreversible.



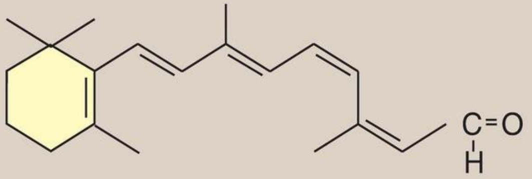
Retinol



Retinal



Retinoic acid (all trans)

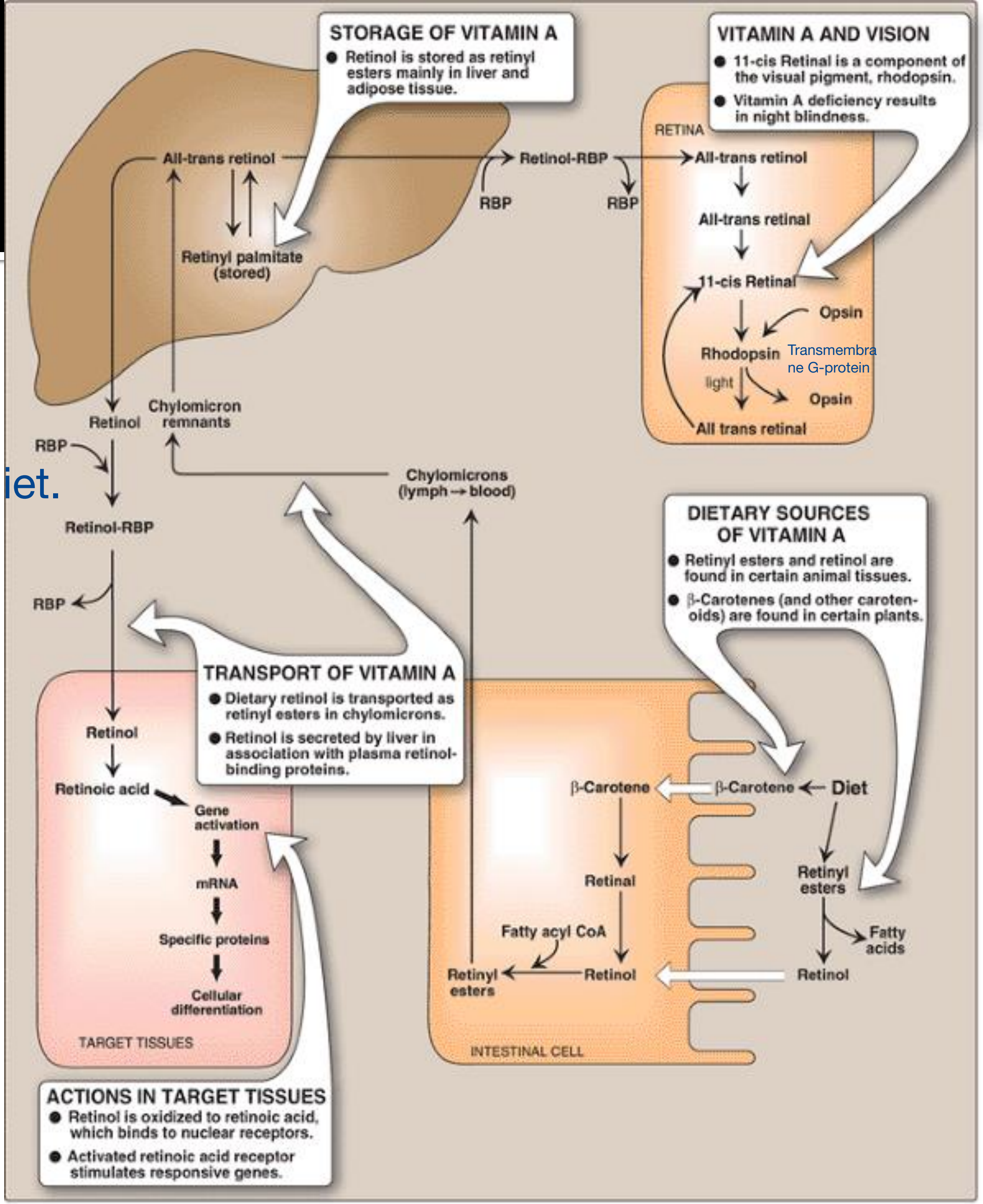


11-cis Retinal (formed by photoisomerization of all-trans retinal)

Absorption & transport

Note the cycle (figure)!!

- ✓ Retinyl esters, intestinal mucosa, retinol
- ✓ Carotenes, retinal, retinol observed from diet.
- ✓ Chylomicrons, lymphatic system, liver (storage)
- ✓ Release from the liver: retinol binds the plasma retinol-binding protein (RBP) complexed with transthyretin
- ✓ Cellular RBP → nuclear receptors (steroids), RNA, proteins (keratin expression)



Visual cycle

- When rhodopsin, a G protein–coupled receptor, is exposed to light, a series of photochemical isomerizations occurs, which results in the bleaching of rhodopsin and release of all-trans retinal and opsin
- This process activates the G protein transducin, triggering a nerve impulse that is transmitted by the optic nerve

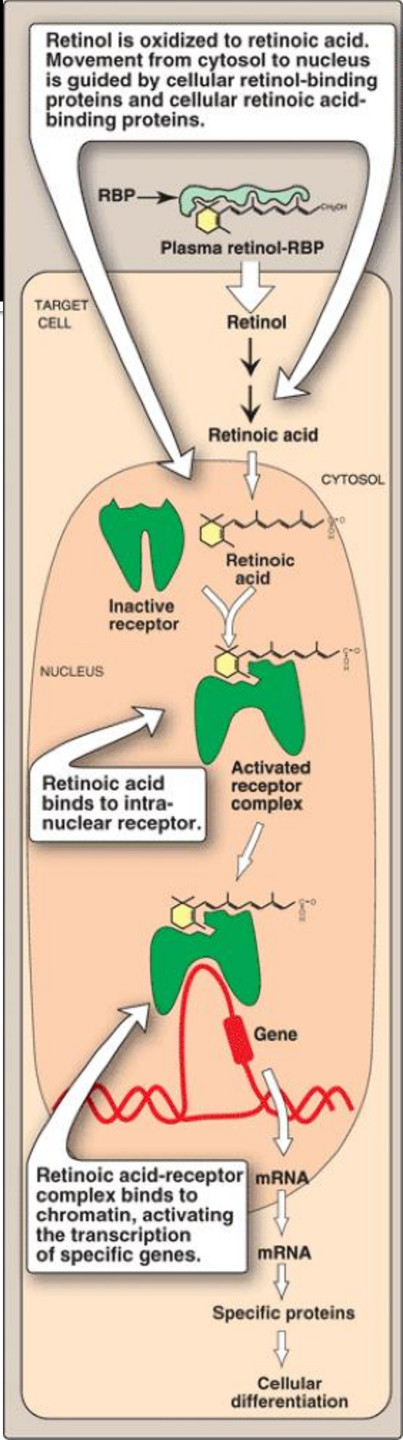
Functions of vitamin A

- ✓ Reproduction: Retinol and retinal (not retinoic acid) are essential for spermatogenesis in the male and preventing fetal resorption in the female
- ✓ Growth (retinoic acid): Vitamin A deficiency results in a decreased (growth rate & bone development) in children
- ✓ Maintenance of epithelial cells (retinoic acid): Vitamin A is essential for normal differentiation of epithelial tissues & mucus secretion
- ✓ Animals given vitamin A only as retinoic acid from birth are blind and sterile

Retinoic acid mechanism of action

Retinoic acid is considered as a setter-point, maybe used in the control of over/under-expressed genes.

- Binds with high affinity [RAR] - nucleus of target tissues such as epithelial cells
- Activated complex binds to response elements on DNA and recruits activators or repressors to regulate retinoid-specific RNA synthesis
- Retinoids control the expression of the gene for keratin in most epithelial tissues of the body
- RAR proteins are part of the superfamily of transcriptional regulators that includes the nuclear receptors for steroid and thyroid hormones and vitamin D (similar way of function)

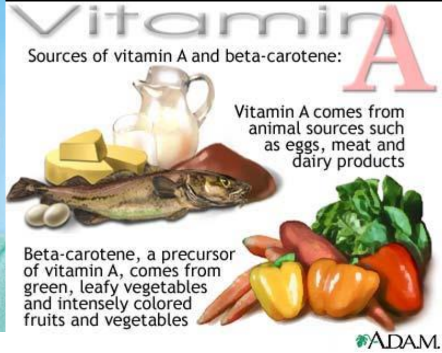


Distribution & Requirements

- Liver, kidney, cream, butter, and egg yolk are good sources of preformed vitamin A
- Yellow, orange, and dark-green vegetables and fruits are good sources of the carotenes (provitamin A)
- RDA for adults is 900 retinol activity equivalents (RAE) for males and 700 RAE for females. In comparison, 1 RAE = 1 µg of retinol or 12 µg of β-carotene

Sources & indications





- Sources: excess cause <u>hypervitaminosis A</u>
- Clinical indications:
  - <u>Dietary deficiency</u>: mild (night blindness, nyctalopia), prolonged (irreversible loss for some visual cells), severe (<u>xerophthalmia</u>) *This is what the prof mentioned in the lecture*
    - Xerophthalmia: ulceration & dryness of conjunctiva & cornea, followed by scar & blindness (affecting over 500,000 children worldwide every year)
  - Acne and psoriasis: effectively treated with retinoic acid

"No need to get into pathology details for now." prof. Nafith :)

Toxicity - Hypervitaminosis A

- Amounts exceeding 7.5 mg/day of retinol should be avoided
- Pregnant women: potential for teratogenesis

Upper-limit

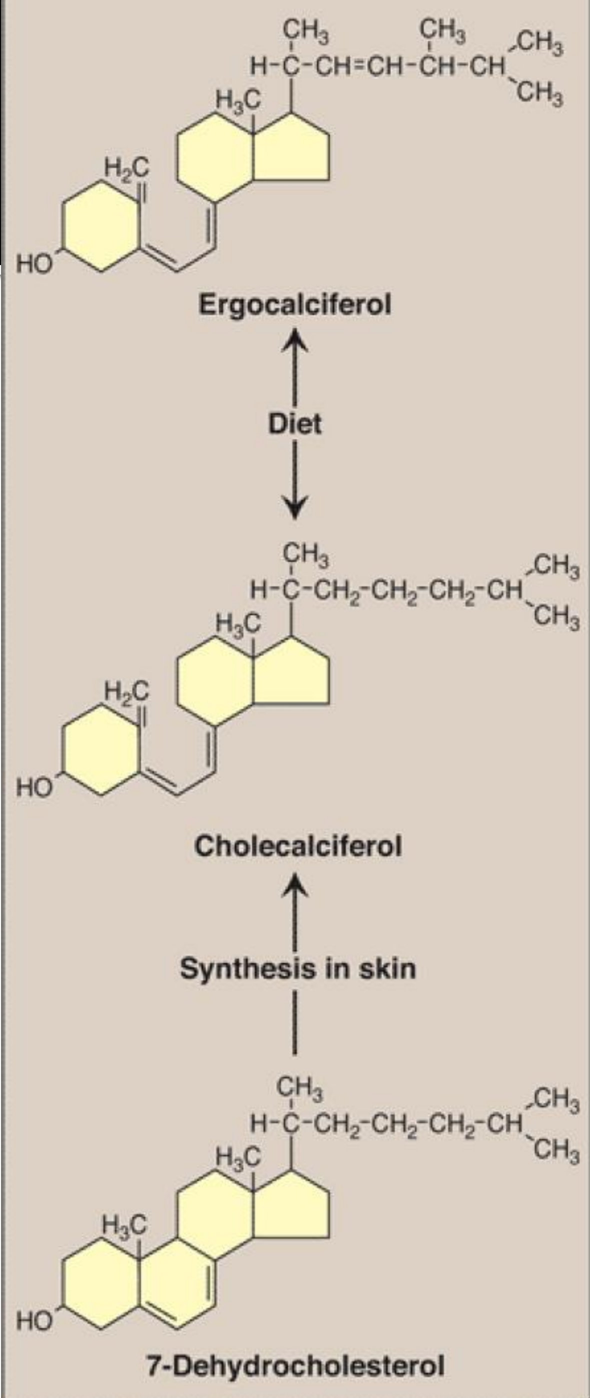
- UL is 3,000 µg of preformed vitamin A/day
- Prolonged treatment with isotretinoin can result in an increase in TAG and cholesterol, providing some concern for an increased risk of CVD

VITAMIN D

- A group of sterols that have a hormone-like function
- Active molecule, 1,25-dihydroxycholecalciferol ([1,25-diOH-D3], or calcitriol), binds to intracellular receptor proteins
- The 1,25-diOH-D3–receptor complex interacts with response elements in the nuclear DNA of target cells (vitamin A) - selectively stimulates or represses gene transcription
- The most prominent actions of calcitriol are to regulate the serum levels of calcium and phosphorus

Distribution

- 1. Endogenous vitamin precursor: 7-Dehydrocholesterol
  - Converted to cholecalciferol and transported to liver bound to vitamin D–binding protein
- 2. Diet: Ergocalciferol (vitamin D2), and cholecalciferol (vitamin D3)
- Differ chemically
- Packaged in chylomicrons
- Preformed vitamin D is a dietary requirement only in individuals with limited exposure to sunlight



Metabolism

- Vitamins D2 and D3 are not biologically active
- Converted in vivo to calcitriol, the active form of vitamin D
- The first hydroxylation (calcidiol)
  - 25 position – liver - 25-hydroxylase
  - The predominant form in serum and the major storage form
- Further hydroxylated
  - 1 position – kidney - 25-hydroxycholecalciferol 1-hydroxylase
  - Formation of 1,25-diOH-D3 (calcitriol)

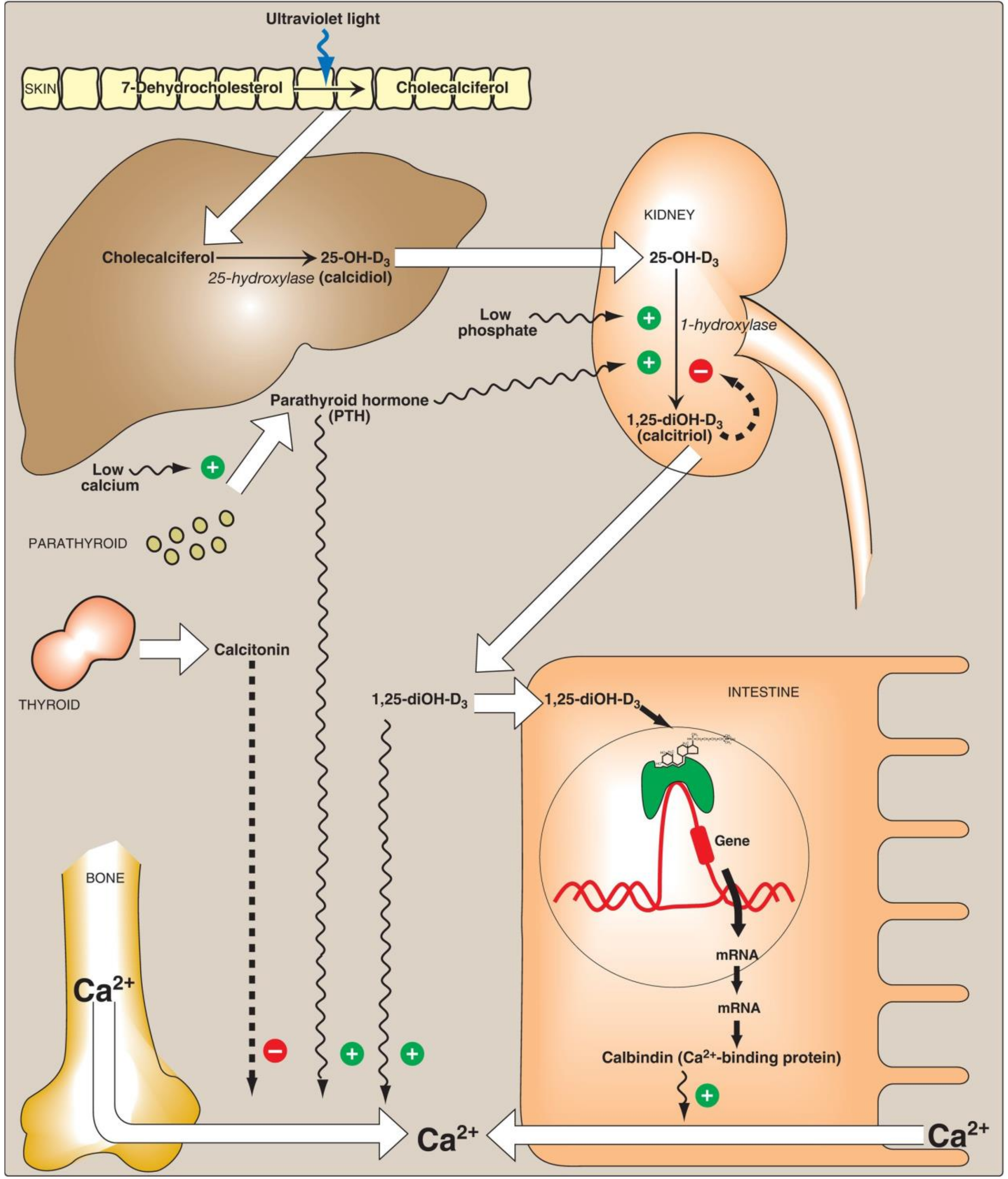
Hydroxylation regulation

- Formation of Calcitriol is tightly regulated by the level of serum phosphate (PO_4^{3-}) and calcium ions (Ca2+)
- *25-Hydroxycholecalciferol 1-hydroxylase* activity is increased
  - Directly by low serum PO_4^{3-}
  - Indirectly by low serum Ca2+ (through PTH)
- Thus, hypocalcemia caused by insufficient dietary Ca2+ results in elevated levels of serum 1,25-diOH-D3
- 1,25-diOH-D3 inhibits expression of PTH, forming a negative feedback loop. It also inhibits activity of the *1-hydroxylase*

Hydroxylation regulation

Most of the regulation occurs at 1-hydroxylase enzyme in the kidney.

(All the regulation details are in the figure, so you know what to do;))



Function

- To **maintain adequate serum levels of Ca2+** (intestine, kidney, and bone)
- Increased expression of the calcium-binding protein calbindin (typical of steroid hormones)

Distribution and requirement

- Naturally in fatty fish, liver, and egg yolk
- Milk, unless it is artificially fortified, is not a good source
- The RDA for individuals ages 1–70 years is 15 µg/day and 20 µg/day if over age 70 years
- 1 µg vitamin D = 40 international units (IU)
- Because breast milk is a poor source of vitamin D, supplementation is recommended for breastfed babies

Toxicity

- High doses (100,000 IU for weeks or months) can cause loss of appetite, nausea, thirst, and weakness
- Enhanced Ca^{2+} absorption and bone resorption results in hypercalcemia, which can lead to deposition of calcium salts in soft tissue (metastatic calcification)
- UL is 100 µg/day (4,000 IU/day) for individuals ages 9 years or older, with a lower level for those under age 9 years
- Toxicity is only seen with use of supplements. Excess vitamin D produced in the skin is converted to inactive forms

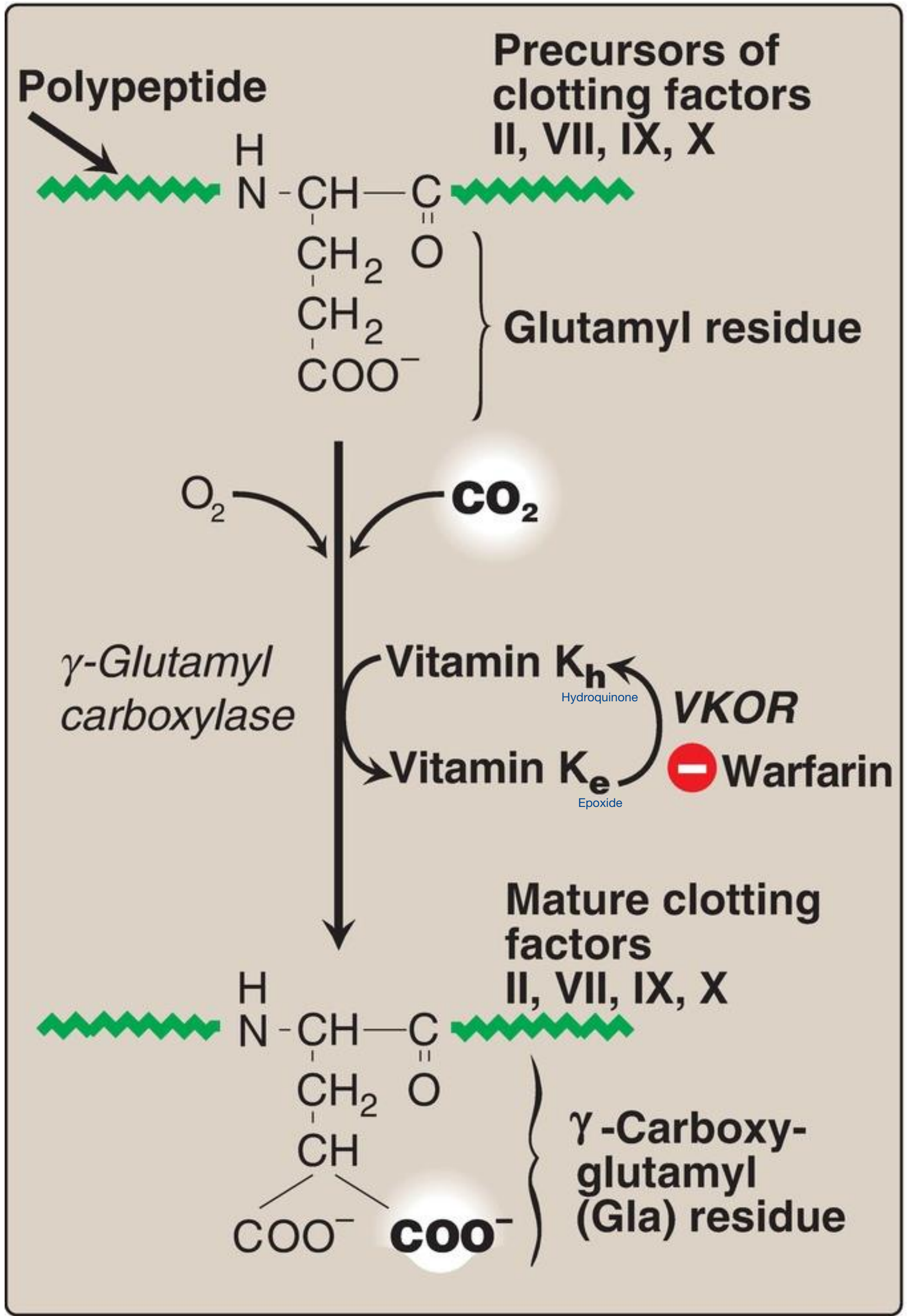
VITAMIN K

- The principal role is in the posttranslational modification of a number of proteins (most of which are involved with blood clotting), in which it serves as a coenzyme in the carboxylation of certain glutamic acid residues in these proteins
- Vitamin K exists in several active forms
- In plants as phylloquinone (or vitamin K_1), and in intestinal bacteria as menaquinone (or vitamin K_2).
- A synthetic form of vitamin K, menadione, is able to be converted to K_2

Function

Injury; exposure to atmospheric oxygen induces the synthesis of clotting factors.

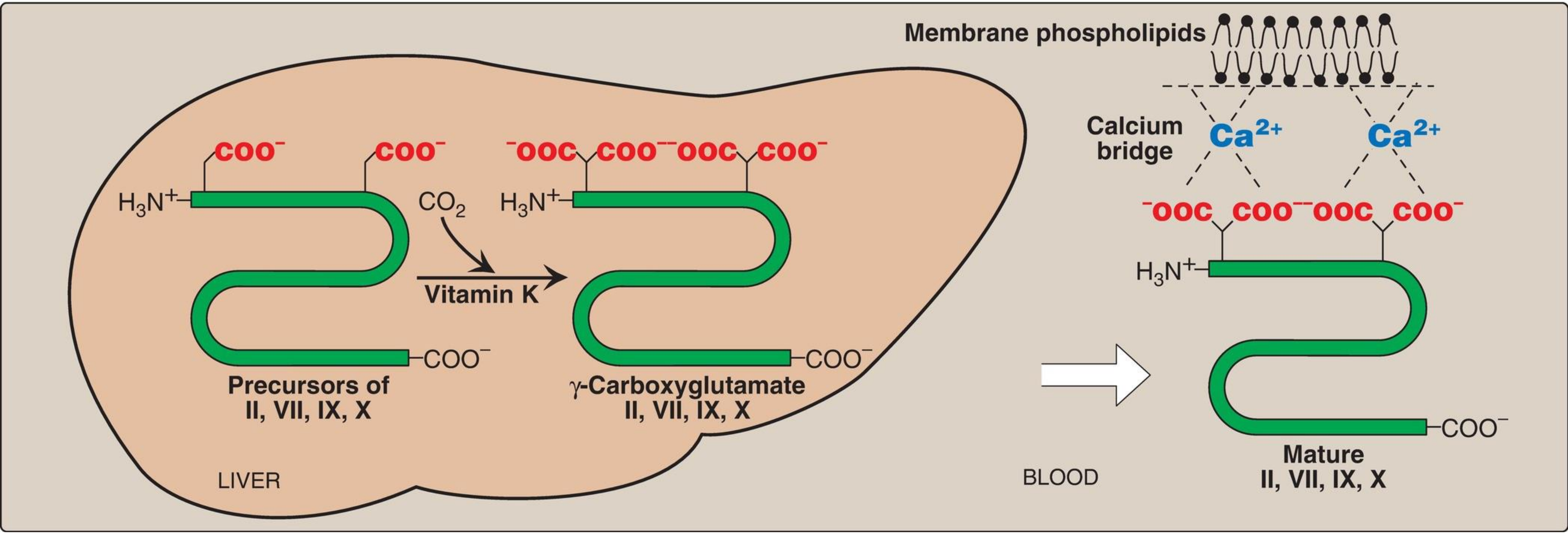
- γ-Carboxyglutamate formation: Vitamin K is required in the hepatic synthesis of the blood clotting proteins, prothrombin (factor [F]II) and FVII, FIX, and FX
- The carboxylation reaction requires γ-glutamyl carboxylase, O_2, CO_2, and the hydroquinone form of vitamin K (which gets oxidized to the epoxide form)
- Formation of Gla residues is sensitive to inhibition by warfarin, a synthetic analog of vitamin K that inhibits vitamin K epoxide reductase (VKOR), the enzyme required to regenerate the functional hydroquinone form of vitamin K



Warfarin is widely used as an anticoagulant drug for patients who've had a condition caused by a blood clot.

Function

- Gla residues are good chelators of positively charged calcium ions, because of their two adjacent, negatively charged carboxylate groups
- Prothrombin–calcium complex is able to bind negatively charged membrane phospholipids on the surface of damaged endothelium and platelets
- Attachment to membrane increases the rate at which the proteolytic conversion of prothrombin to thrombin can occur


Membrane phospholipids
Calcium bridge
Ca2+
Ca2+
⁻OOC COO⁻ ⁻OOC COO⁻
H3N+
COO⁻
COO⁻
COO⁻
CO2
Vitamin K
Precursors of
II, VII, IX, X
γ-Carboxyglutamate
II, VII, IX, X
Mature
II, VII, IX, X
LIVER
BLOOD

Distribution and requirement

- Found in cabbage, spinach, egg yolk, and liver
- Adequate intake for vitamin K is 120 µg/day for adult males and 90 µg for adult females
- There is also synthesis of the vitamin by the gut microbiota

Thus, vitamin K is rarely deficient except in certain conditions.

Clinical indications for vitamin K

- 1. Deficiency:
- A true vitamin K deficiency is unusual – long antibiotic treatment
- In addition, certain cephalosporin antibiotics (for example, cefamandole) cause hypoprothrombinemia, apparently by a warfarin-like mechanism that inhibits *VKOR*. Consequently, their use in treatment is usually supplemented with vitamin K

Clinical indications for vitamin K

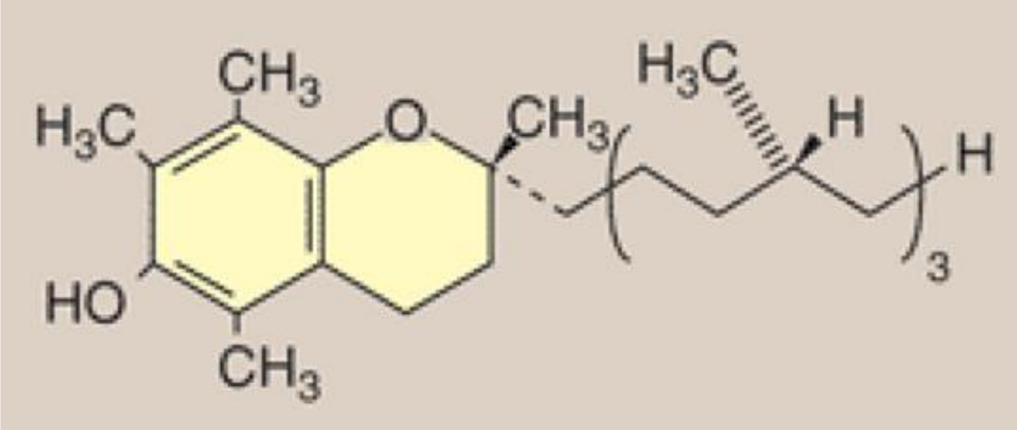
- 2. Deficiency in the newborn: sterile intestines. Human milk provides only about one fifth of the daily requirement for vitamin K, it is recommended that all newborns receive a single intramuscular dose of vitamin K as prophylaxis against hemorrhagic disease of the newborn

Toxicity

- Prolonged administration of large doses of menadione can produce hemolytic anemia and jaundice in the infant, because of toxic effects on the RBC membrane
- Therefore, it is no longer used to treat vitamin K deficiency
- No UL for the natural form has been set

Vitamin E

- ✓ 8 naturally occurring tocopherols
- ✓ α-tocopherol is the most active form
- ✓ The primary function is as an antioxidant (Ring structure)
- ✓ Vitamin E deficiency is almost entirely restricted to premature infants
- ✓ When observed in adults, it is usually associated with defective lipid absorption or transport



Good Luck :)