Lipid-soluble vitamins

+ *Vitamin B12 and folate*

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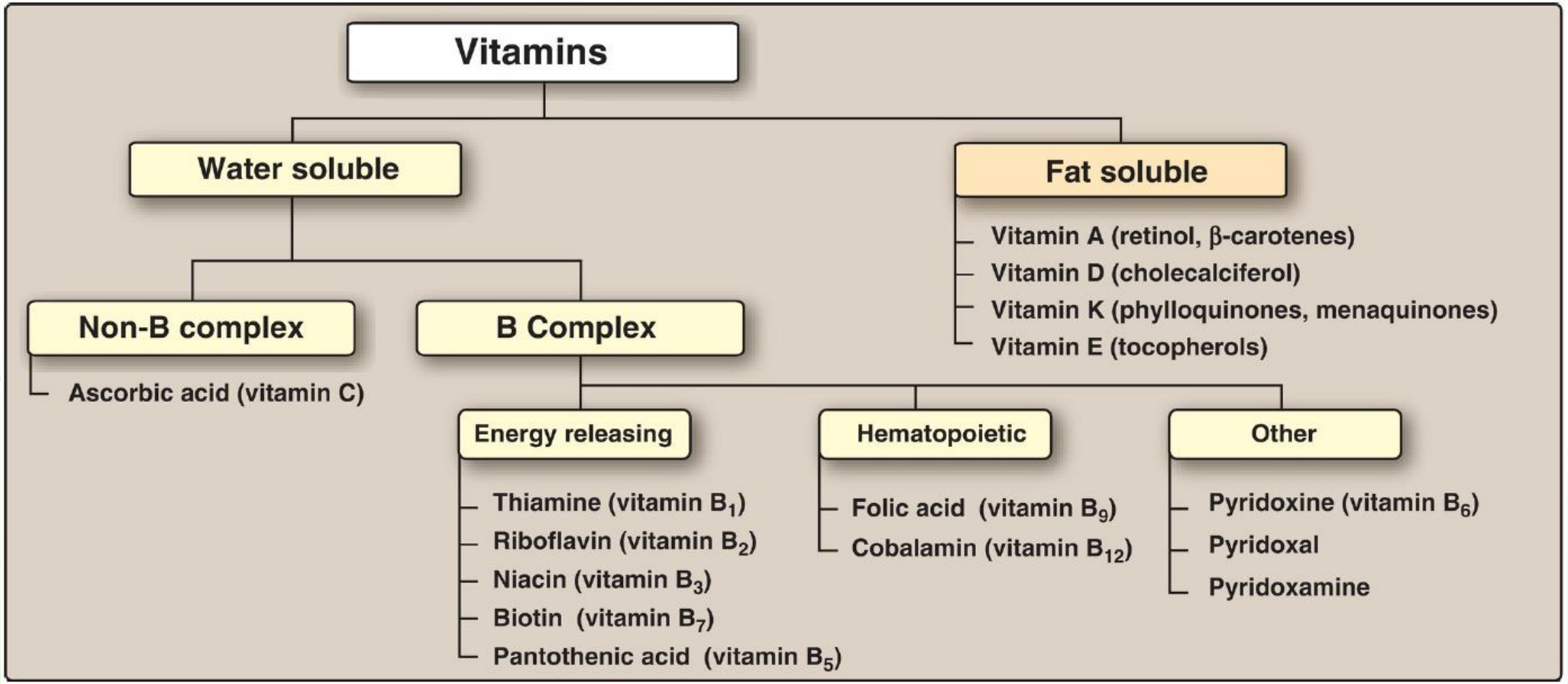
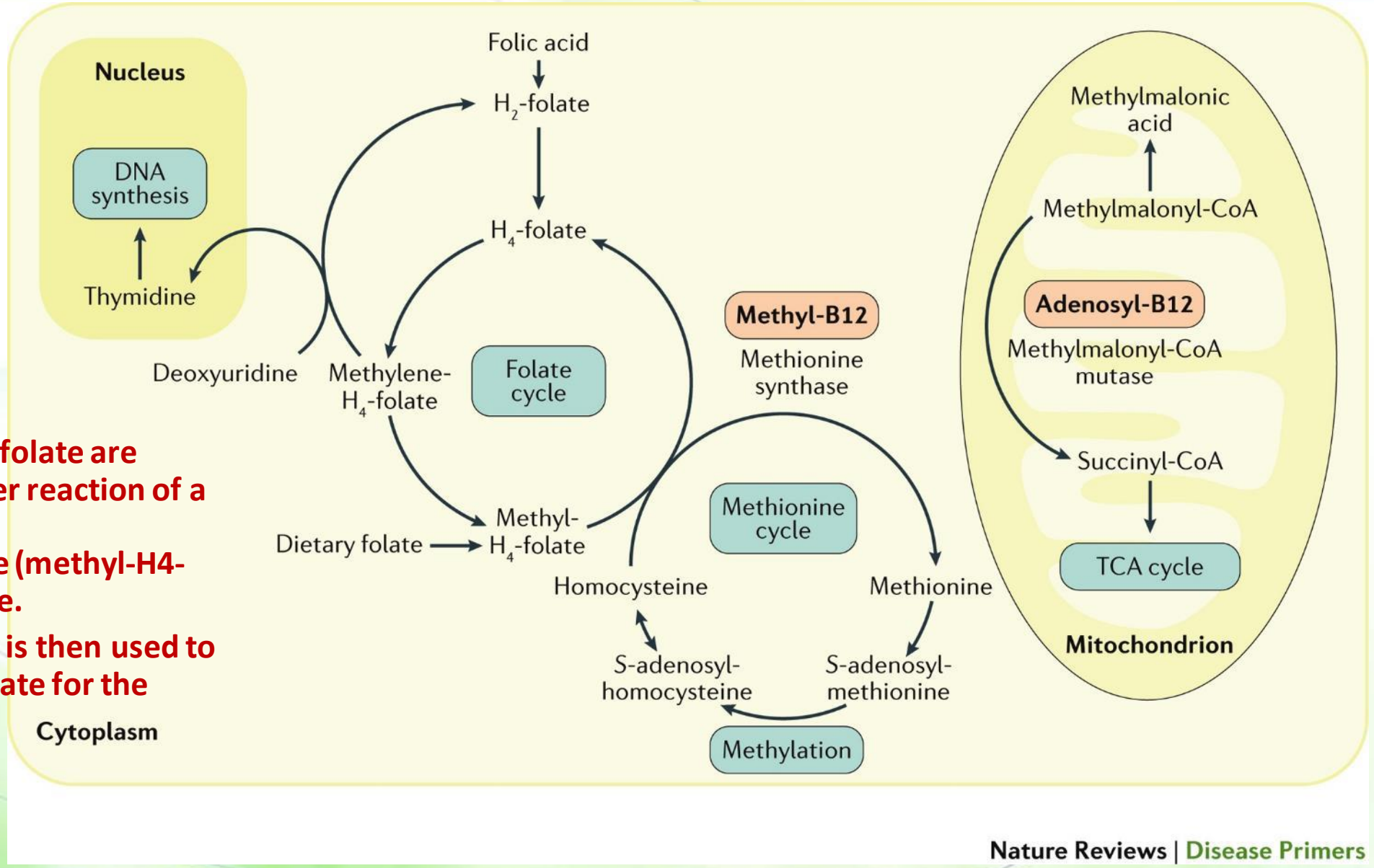
Vitamins

- They are organic compounds an organism requires in low amounts as vital nutrients.
- They cannot be synthesized in sufficient quantities & and must be obtained from diet.
- Thirteen vitamins are universally recognized at present.
- They have diverse biochemical functions:
  - Hormone-like functions (regulators): regulators of mineral metabolism (e.g., vitamin D), or regulators of cell & and tissue growth & and differentiation (e.g., vitamin A)
  - Anti-oxidants (e.g., vitamins E & C)
  - Precursors for enzyme cofactors (vitamin B subclasses)

Classification



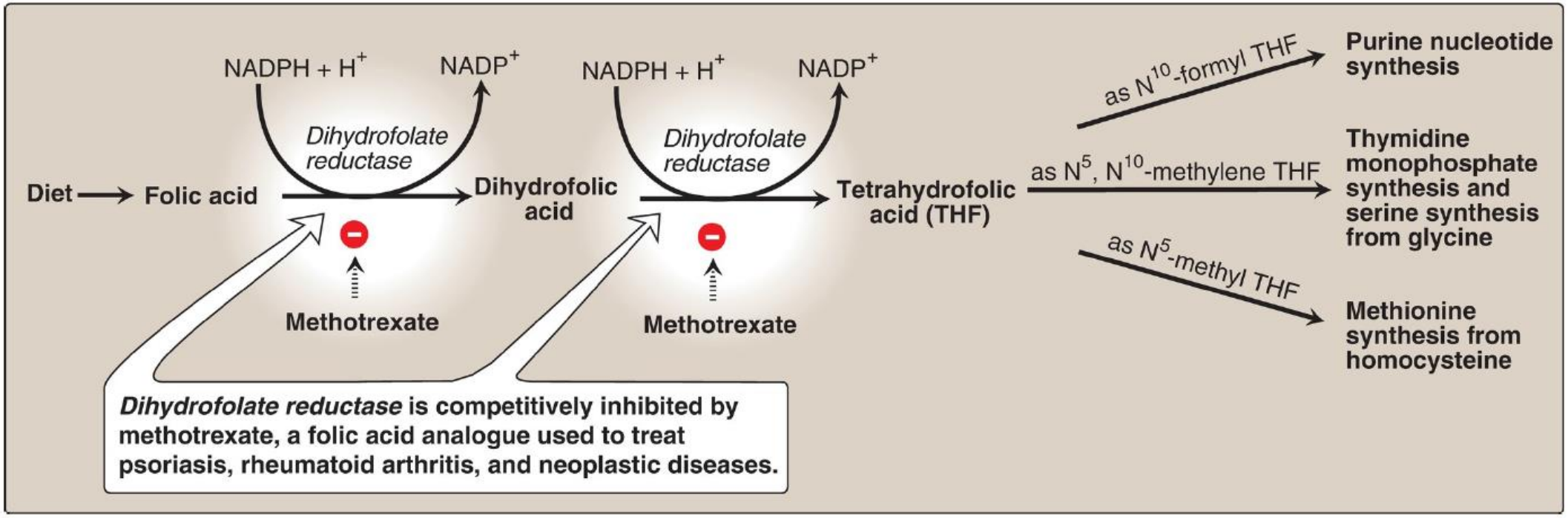
The connection between folate and vitamin B12



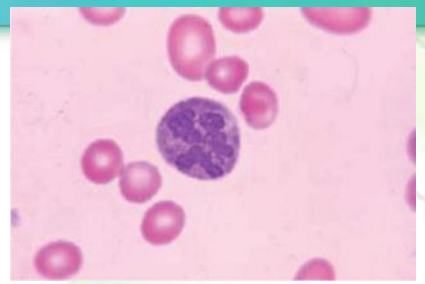
- **Vitamin B12 (B12) and folate are required for the transfer reaction of a methyl group from methyltetrahydrofolate (methyl-H4-folate) to homocysteine.**
- **The resulting H4-folate is then used to make methylene-H4folate for the synthesis of thymidine**

Folic acid (folate or vitamin B9)

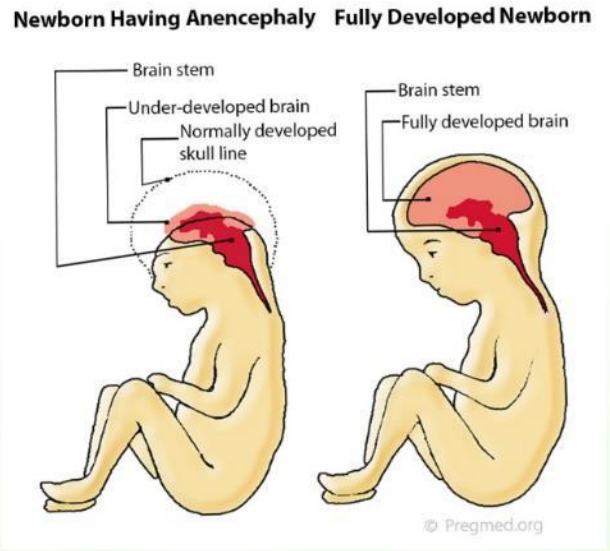
- Folate mediates one-carbon transfer from donors such as serine, glycine, and histidine to intermediates during the synthesis of amino acids, purine nucleotides, and thymidine monophosphate (TMP).
- The active form of folate is the reduced tetrahydrofolate (THF).



Folate and anemia



- Causes of deficiency:
  - Increased demand (pregnancy and lactation)
  - Poor absorption (pathology or alcoholism)
  - Drugs (methotrexate)
  - Folate-free diet (few weeks)
- Deficiency might result in:
  - Megaloblastic anemia: no synthesis of purine nucleotides and TMP → cells cannot make DNA → no cell division.
  - Neural tube defects (NTD): Spina bifida and anencephaly



Folate supplementation

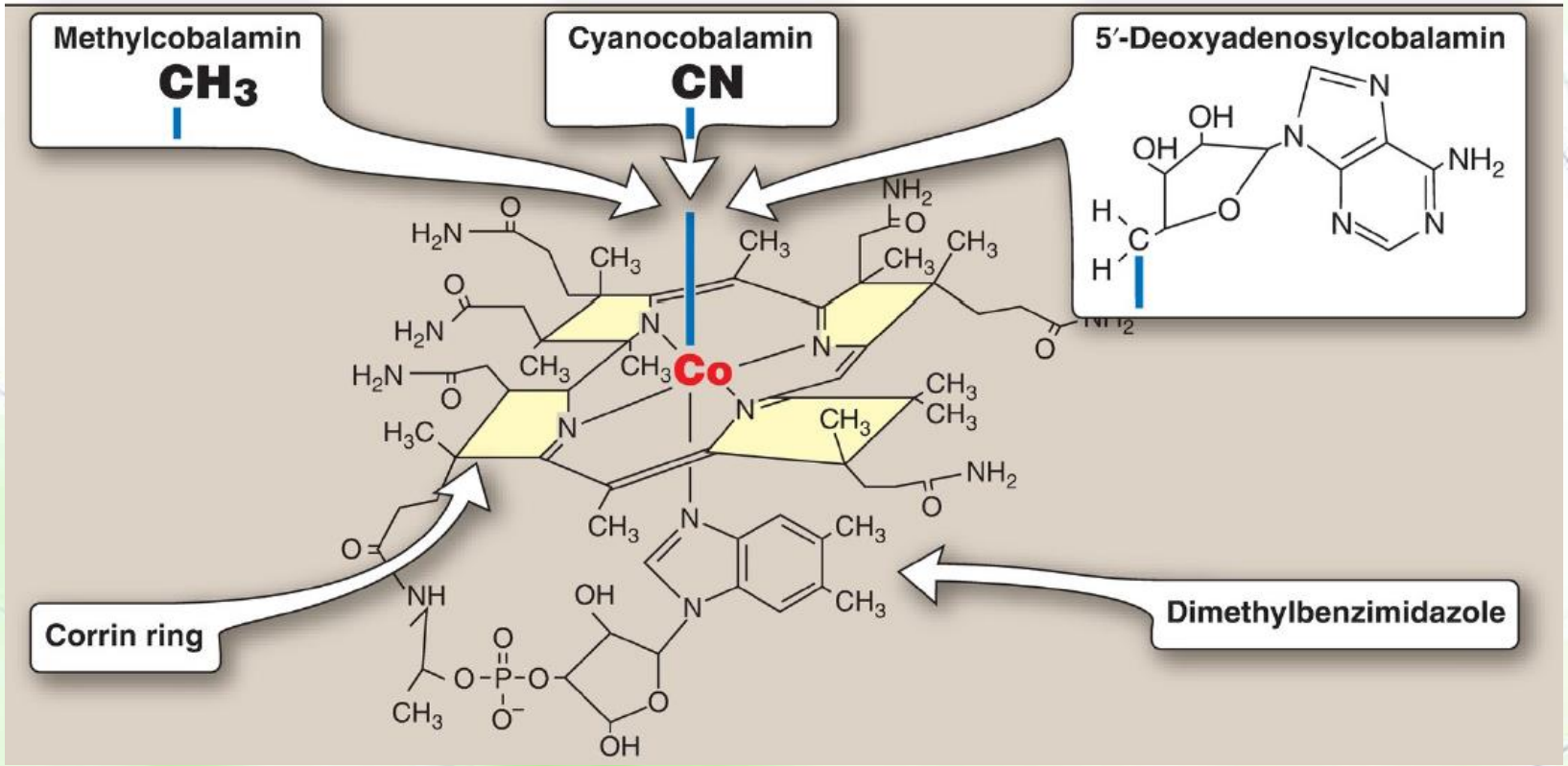
- Folic acid supplementation before conception and during the first trimester is needed.
- All women of childbearing age need 400 µg/day of folic acid to reduce the risk
  - 10 times if a previous pregnancy was affected.
- In the U.S., folic acid is added to wheat flour and enriched grain products, resulting in a dietary supplementation of ~100 µg/day.

Cobalamin (vitamin B12)

Structure and coenzyme forms

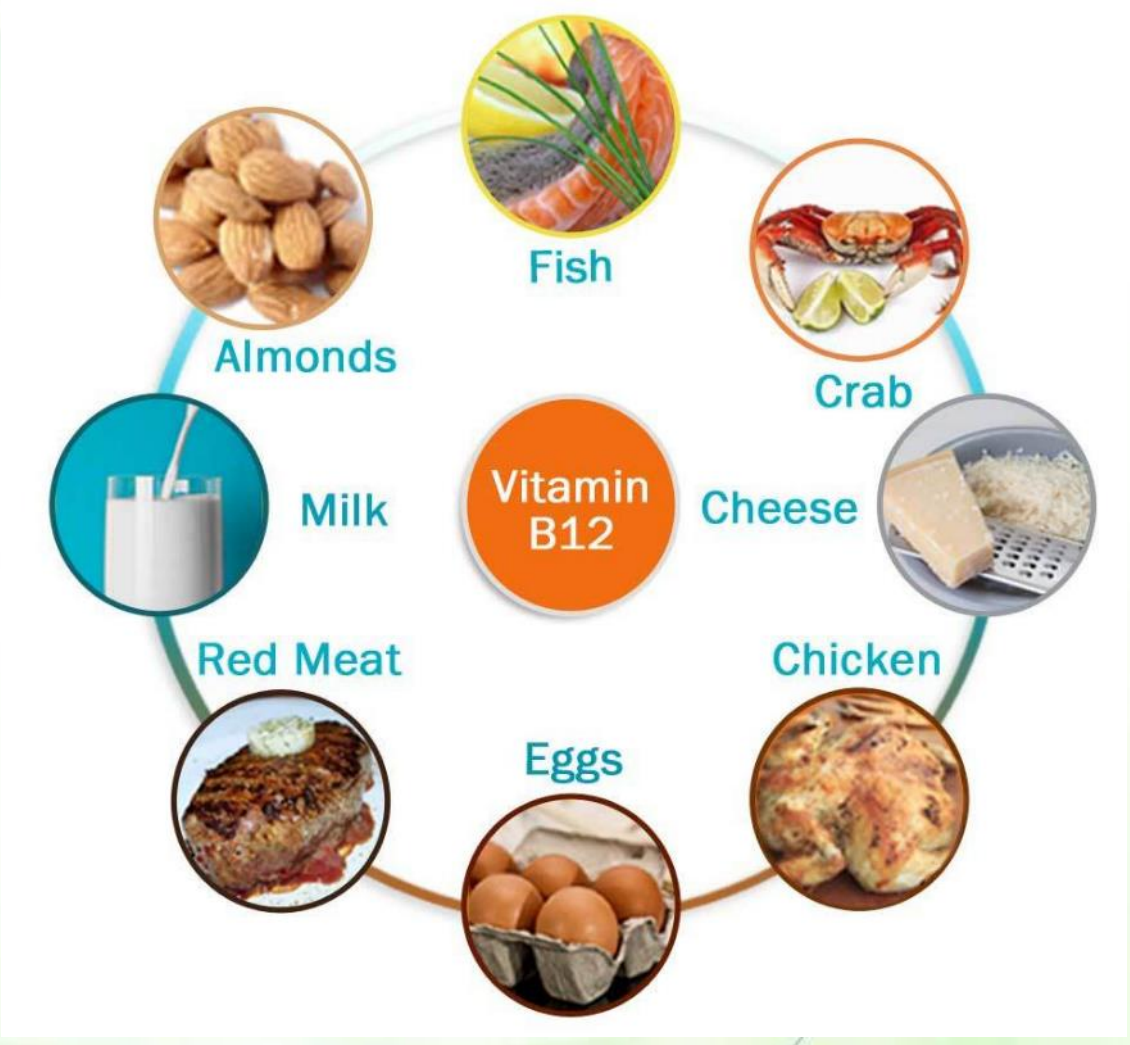
- It contains a “corrin” ring that looks like a pyrrole ring.
- The physiologic coenzymes are: *5’-deoxyadenosylcobalamin and methylcobalamin*
- The commercial form has a cyanide is added (cyanocobalamin).

Not important



Sources of cobalamin

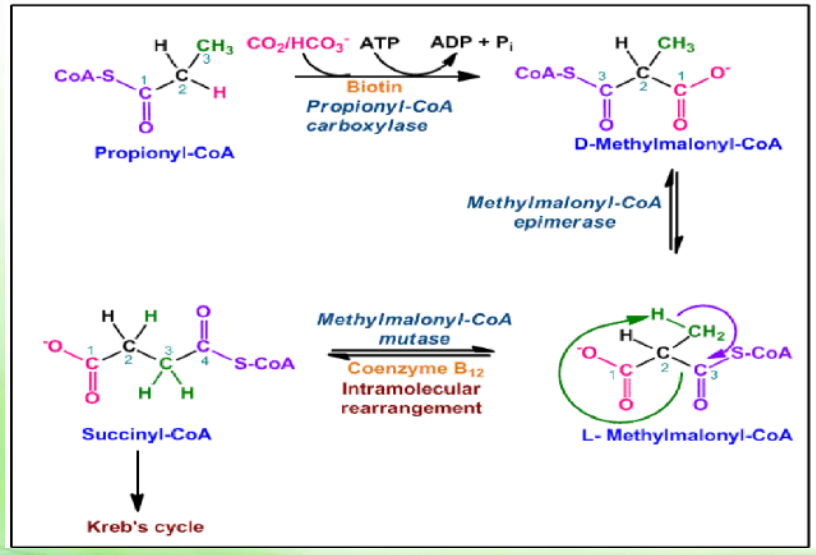
- Vitamin B12 is synthesized only by intestinal microbiota or by eating foods derived from other animals, but not from plants.
- Cobalamin is present in good amounts in liver, red meat, fish, eggs, dairy products, and fortified cereals.

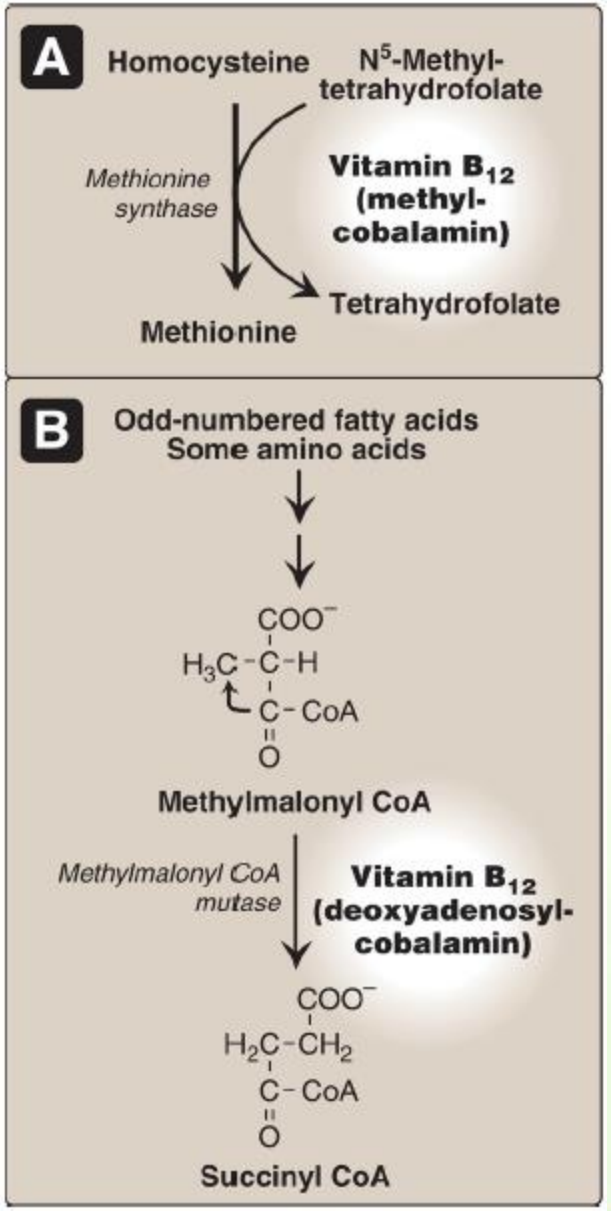


Biochemical need of cobalamin (vitamin B12)

- It is required for two essential enzymatic reactions:
  - Re-methylation of homocysteine (Hcy) to methionine
  - Isomerization of methylmalonyl coenzyme A (CoA) during:
    - Degradation of some amino acids (methionine and the branched isoleucine, valine, and threonine)
    - Degradation of fatty acids (FA) with odd numbers of carbon atoms.

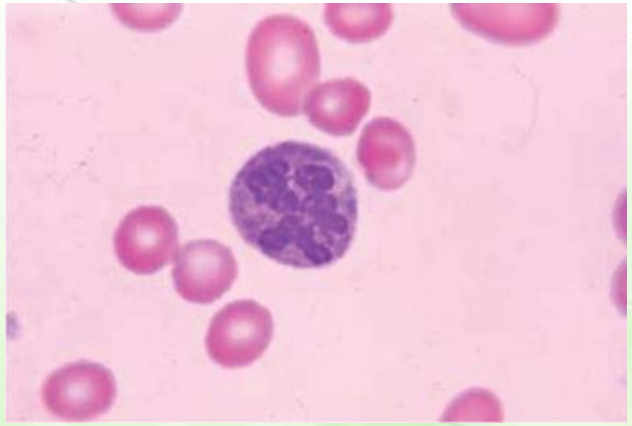
- When deficient,
  - Branched FAs accumulate resulting in neurologic manifestations of vitamin B12 deficiency.
  - Homocysteine is not re-methylated resulting in its accumulation.

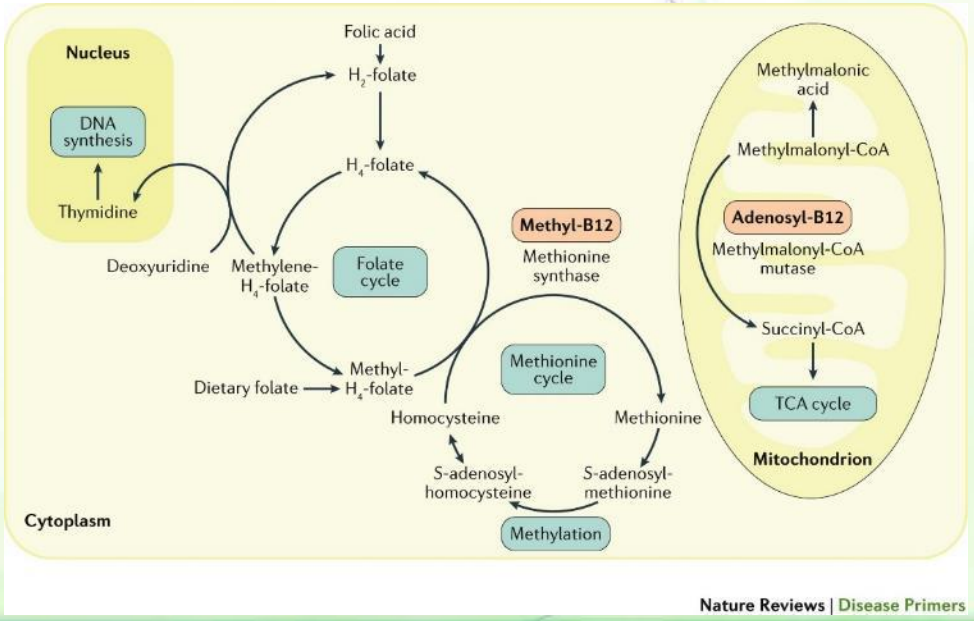




Folate trap hypothesis

- Cobalamin deficiency affects rapidly dividing cells, such as the erythropoietic tissue of bone marrow and the mucosal cells of the intestine since they need both the N5,N10-methylene and N10-formyl forms of THF for the synthesis of nucleotides.
- In cobalamin deficiency, the utilization of the N5-methyl form of THF is impaired and, hence, it accumulates.
- Deficiency of THF forms results in megaloblastic anemia.



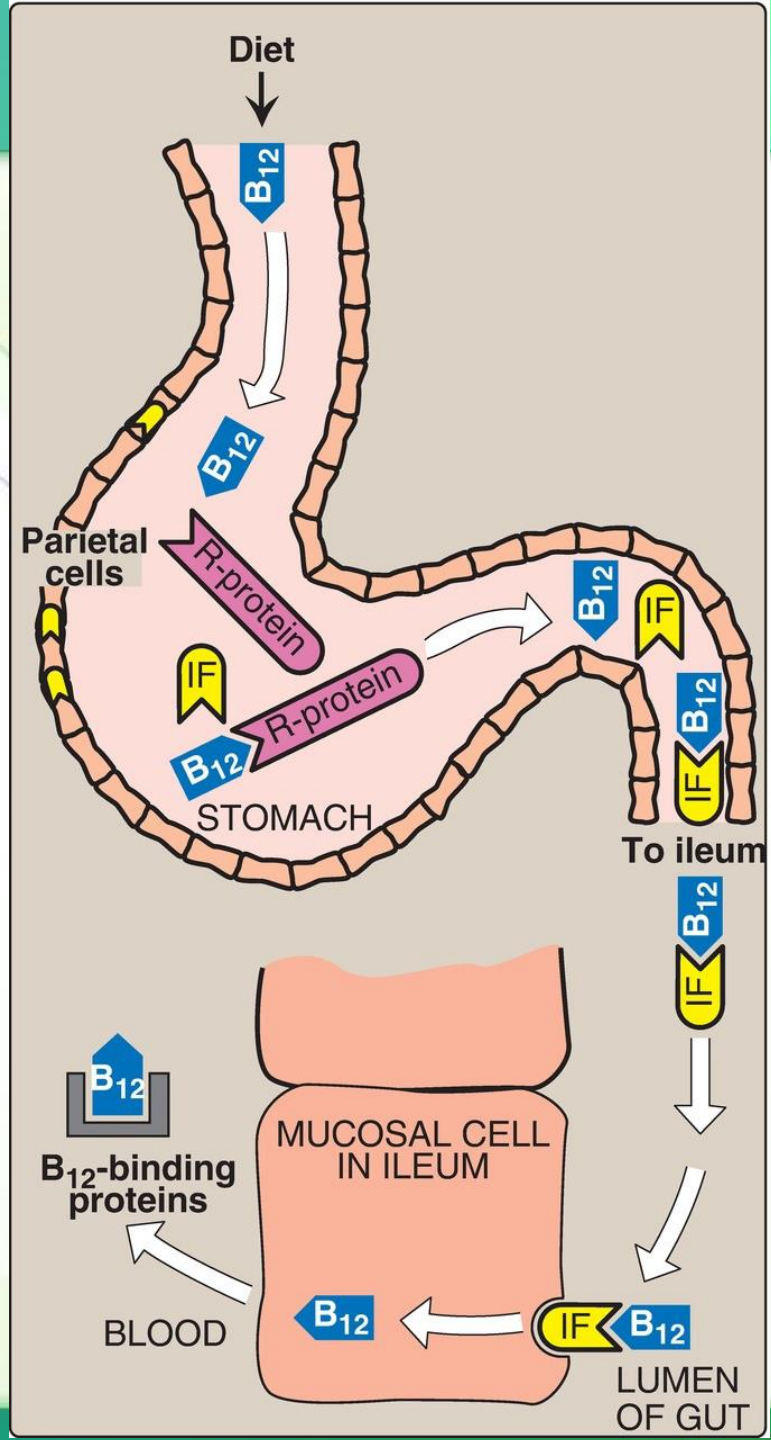


Clinical indications for cobalamin

- In contrast to other water-soluble vitamins, significant amounts (2–5 mg) of vitamin B12 are stored in the body.
- Clinical symptoms may develop after several years of deficiency.
- Deficiency happens much more quickly (in months) if absorption is impaired.

Absorption of vitamin B12 and Pernicious anemia

- Severe malabsorption of vitamin B12 leads to pernicious anemia.
  - *Pernicious: harmful gradually and subtly.*
- It is, most commonly, a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of intrinsic factor (IF), which is a protein that helps in its absorption in the intestines via binding to a receptor called cubilin.
- Malabsorption in the elderly causes achlorhydria (no HCl).
- Individuals with cobalamin deficiency are usually anemic (folate recycling is impaired).

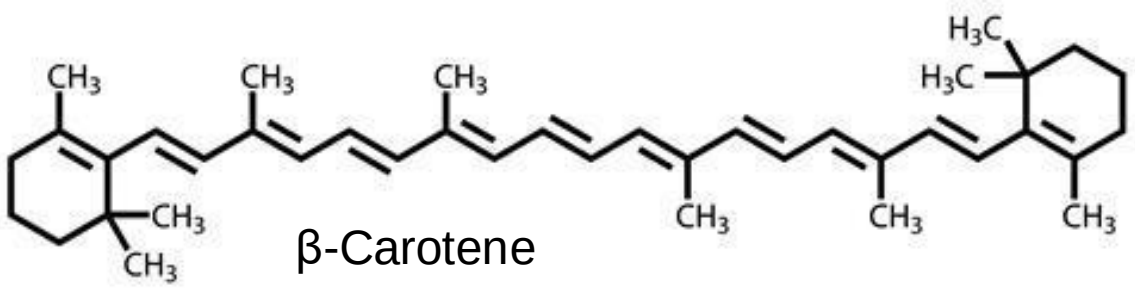


Lipid-soluble vitamins

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

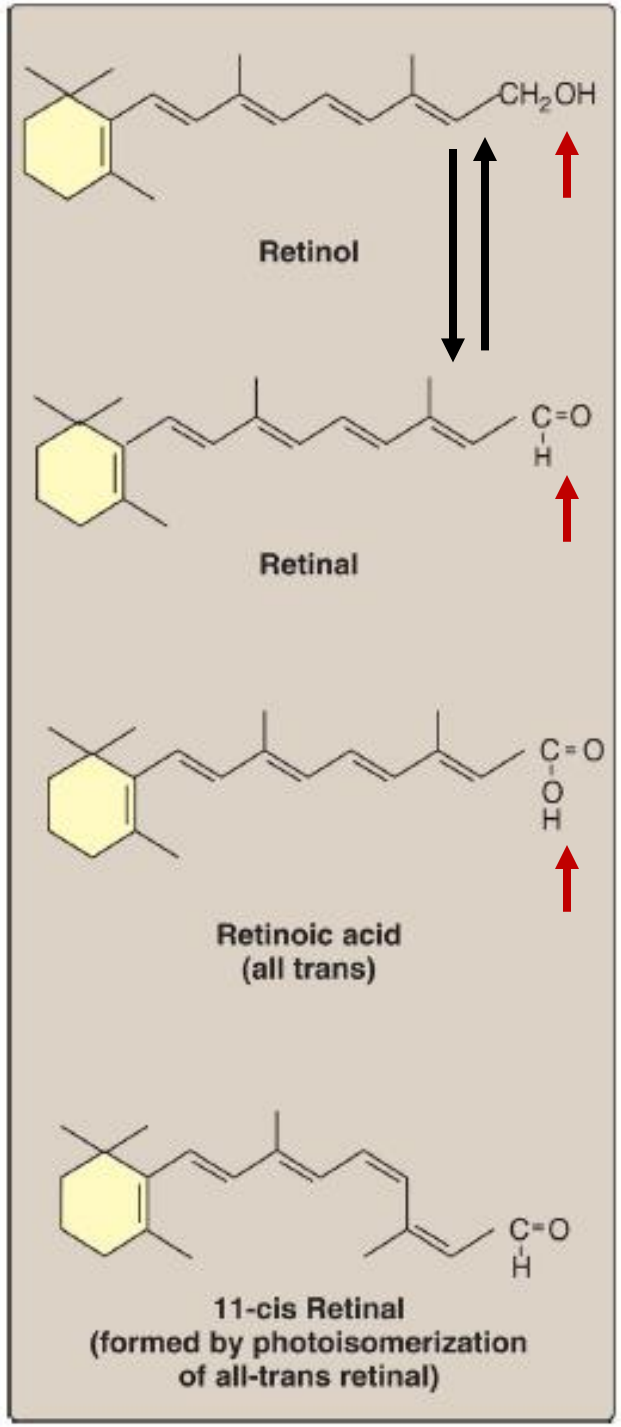
All fat-soluble vitamins are carried in chylomicrons.

Vitamin A



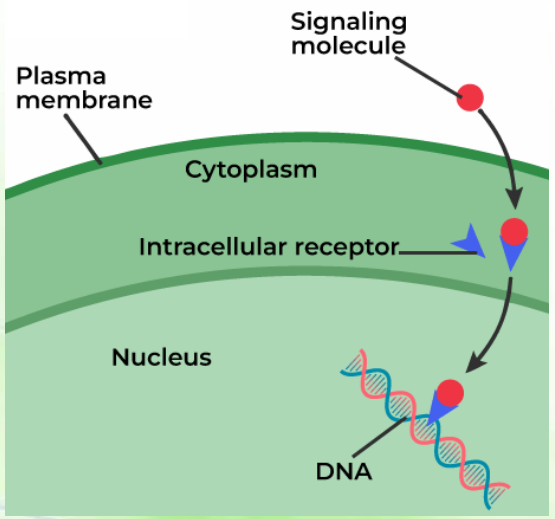
β-Carotene

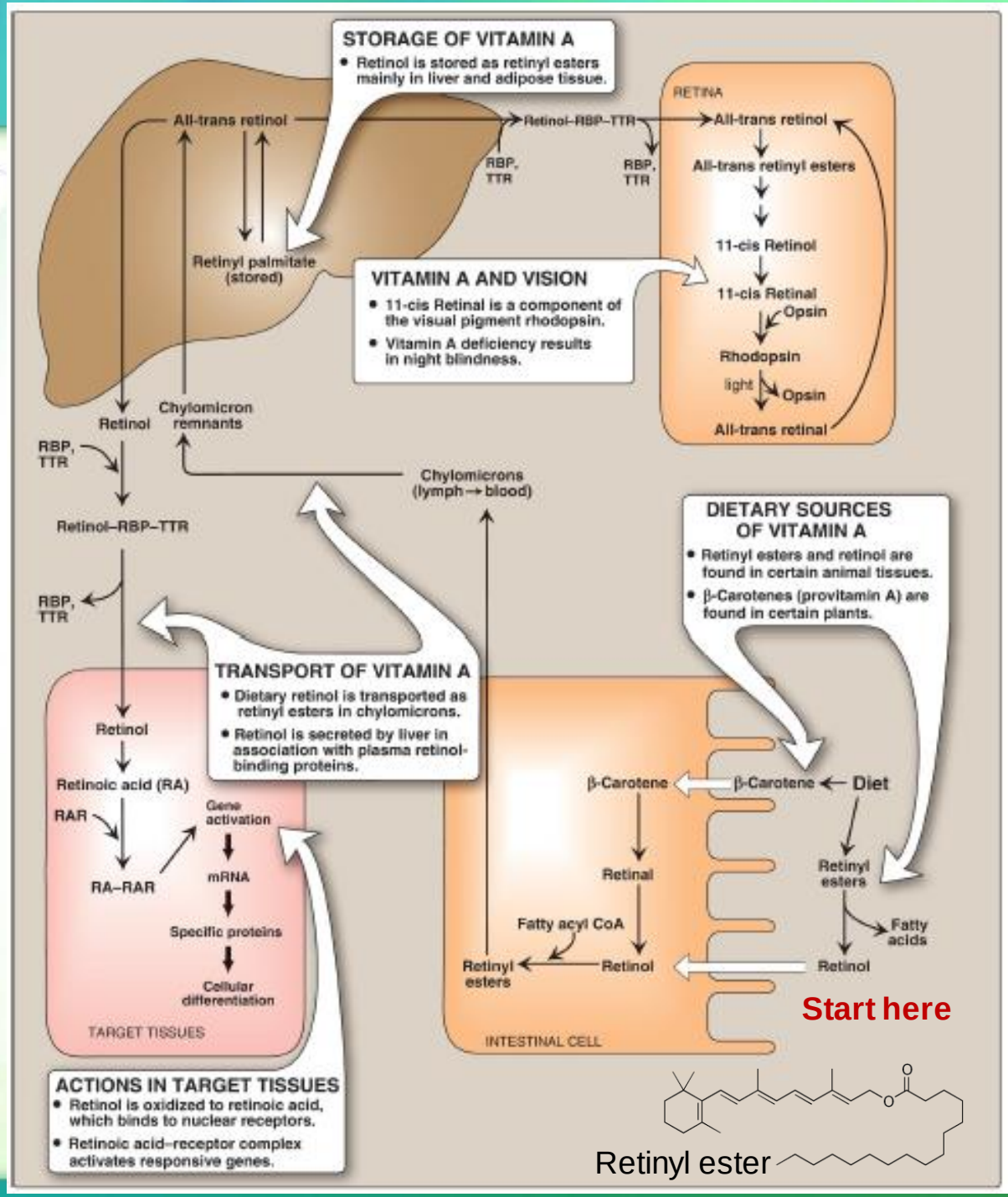
- The retinoids are different forms of vitamin A.
- They are derived from β-Carotene, which is oxidatively cleaved in the intestines to yield 2 molecules of retinal.
- Retinal and retinol are inter-convertible.
- Retinoic acid mediates most of the actions of the retinoids, except for vision and spermatogenesis.



Absorption & transport

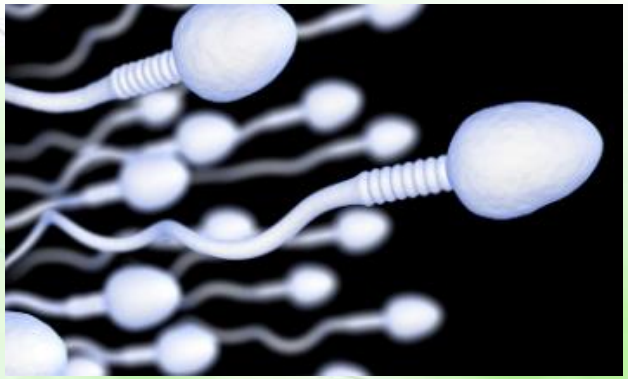
- Intestinal cells absorb β-Carotene and retinol (from retinyl esters), then re-esterified.
- Retinal esters are transported to the liver via chylomicrons for storage.
- Retinol binds the plasma retinol-binding protein (RBP) complexed with transthyretin for transport and entry into target cells.
- In the retina, retinol is oxidized to retinoic acid, which is involved in vision.
- In other target cells, retinol is oxidized to retinoic acid, which binds to intracellular receptors and the complex binds to DNA elements regulating transcription.
- Example: the keratin genes in most epithelial tissues





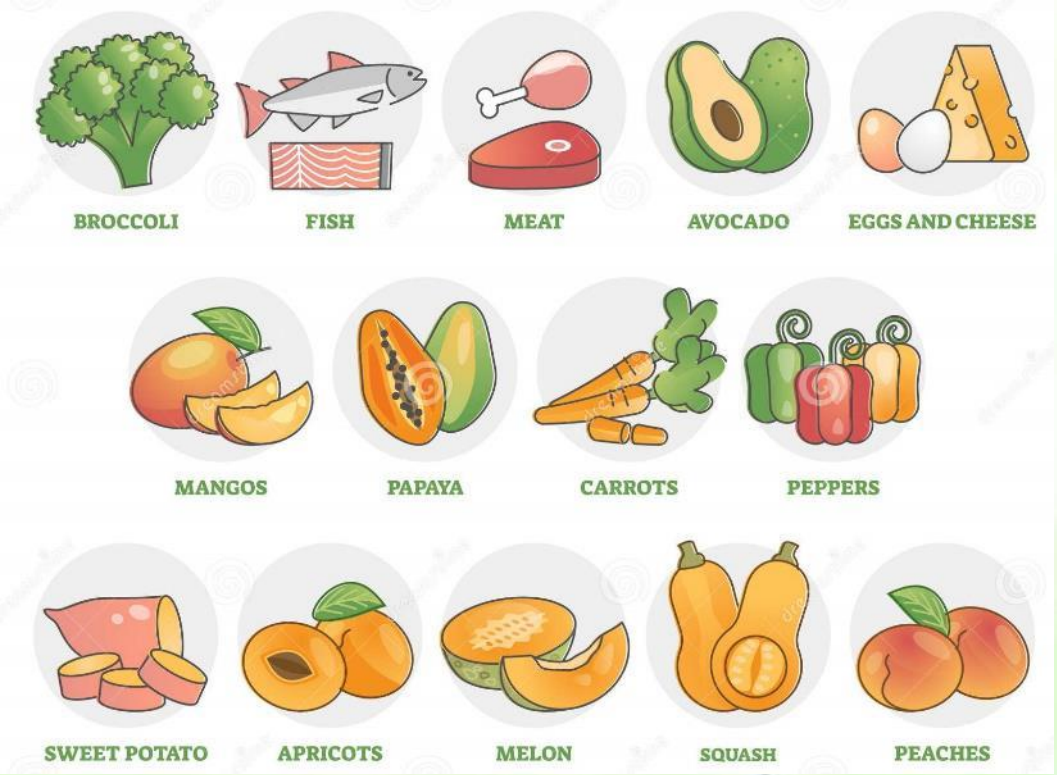
Functions of vitamin A

- 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 and bone development) in children.
- Maintenance of epithelial cells (retinoic acid): Vitamin A is essential for normal differentiation of epithelial tissues & and mucus secretion.
- Animals given vitamin A only as retinoic acid from birth are blind and sterile.



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 β-carotene (provitamin A).



Dietary deficiency of vitamin A

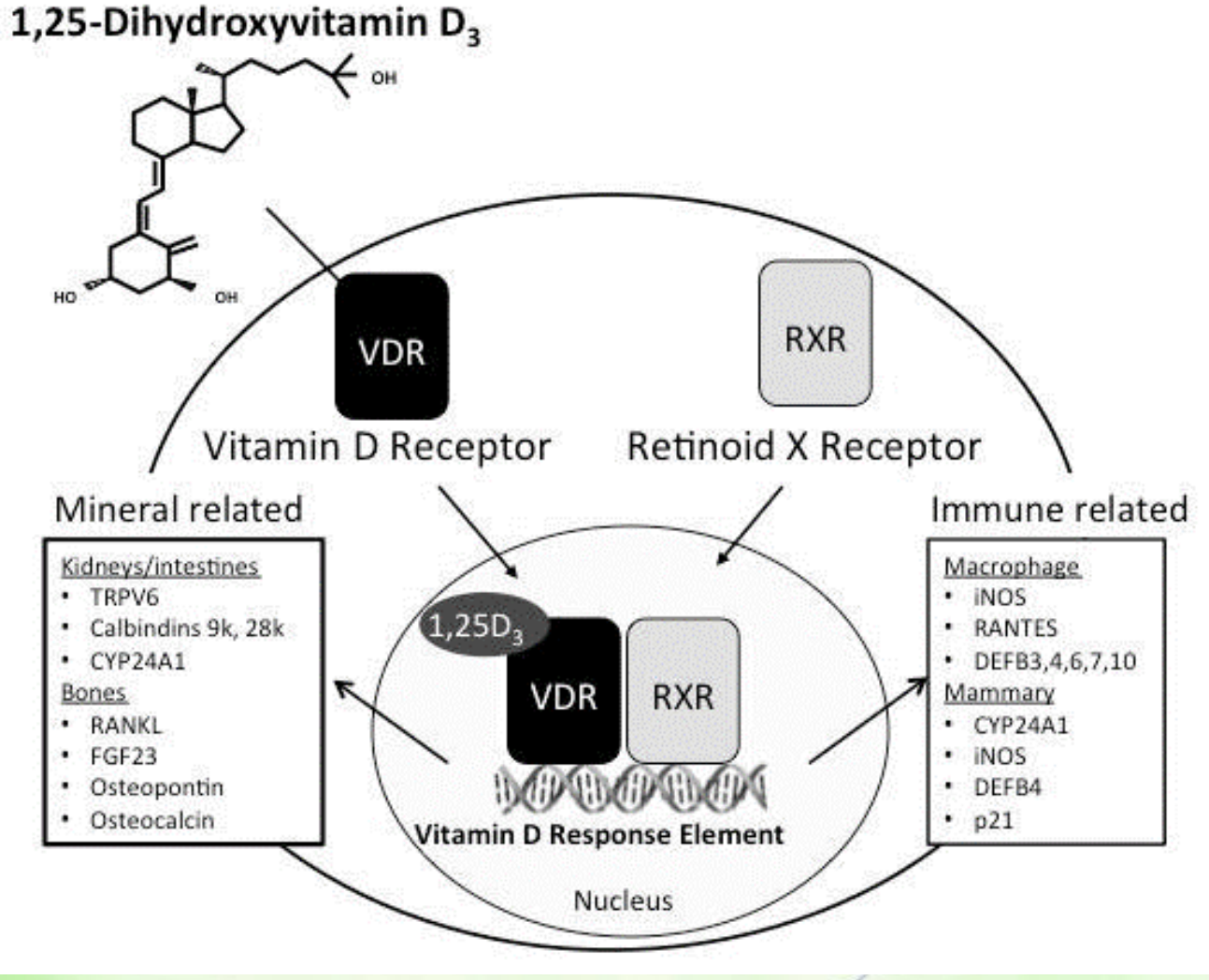
- Mild (night blindness, nyctalopia)
  - *Night=nyx, blind=alaos, eye=ōps*
- Prolonged (irreversible loss for some visual cells)
- Severe (xerophthalmia)
  - Xerophthalmia: ulceration & dryness of conjunctiva & cornea, followed by scar & blindness (affecting over 500,000 children worldwide every year)
  - Acne and psoriasis: effectively treated with retinoic acid

Toxicity - Hypervitaminosis A

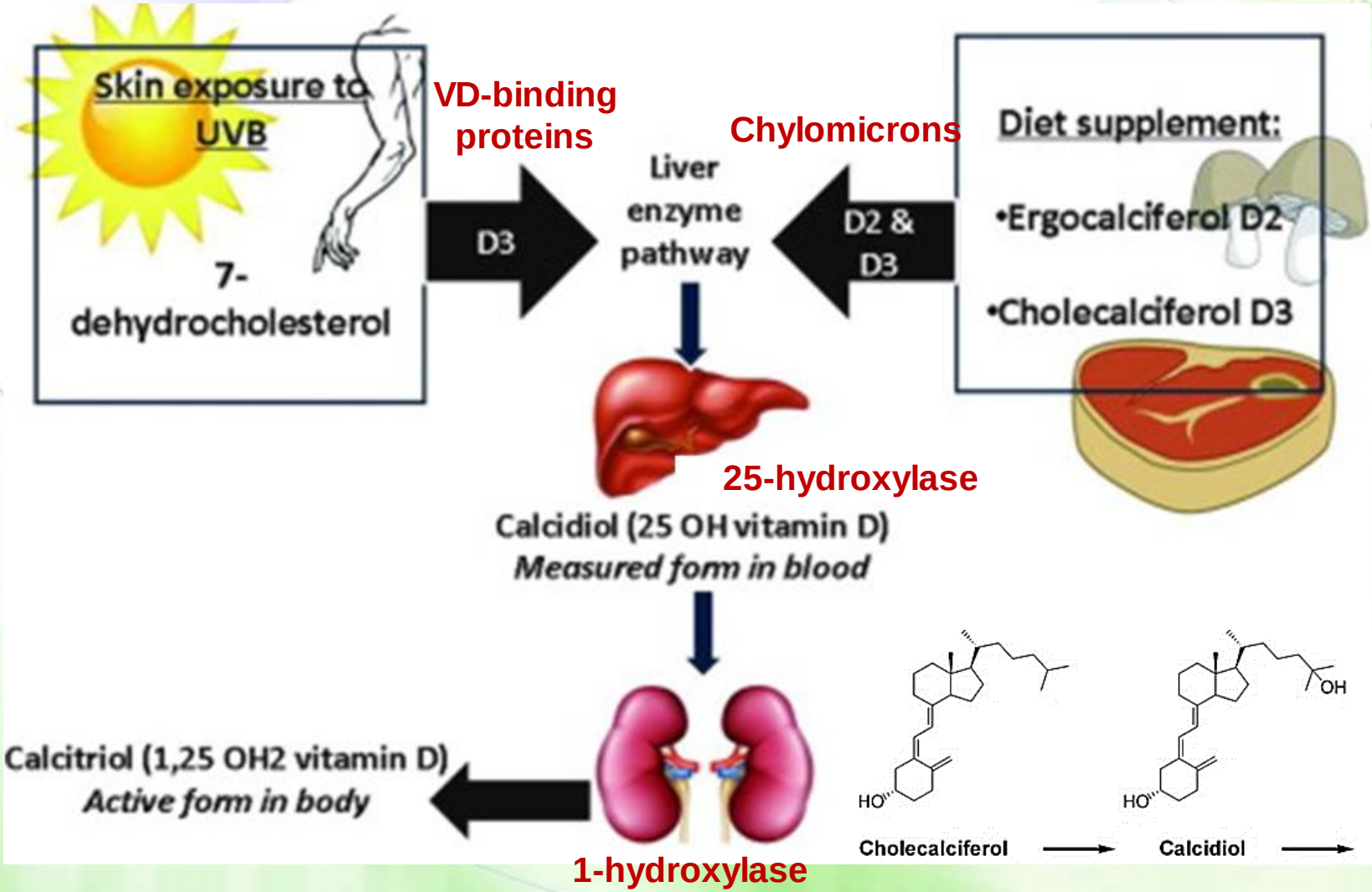
- Excess vitamin A causes hypervitaminosis A.
- The upper limit is 3 mg of preformed vitamin A/day
- Amounts exceeding 7.5 mg/day of retinol should be avoided.
- Pregnant women are at risk of teratogenesis
  - Congenital malformations are produced in an embryo or fetus.
- Prolonged treatment with isotretinoin (an isomer of retinoic acid) can increase TAG and cholesterol, providing some concern for an increased risk of CVD.

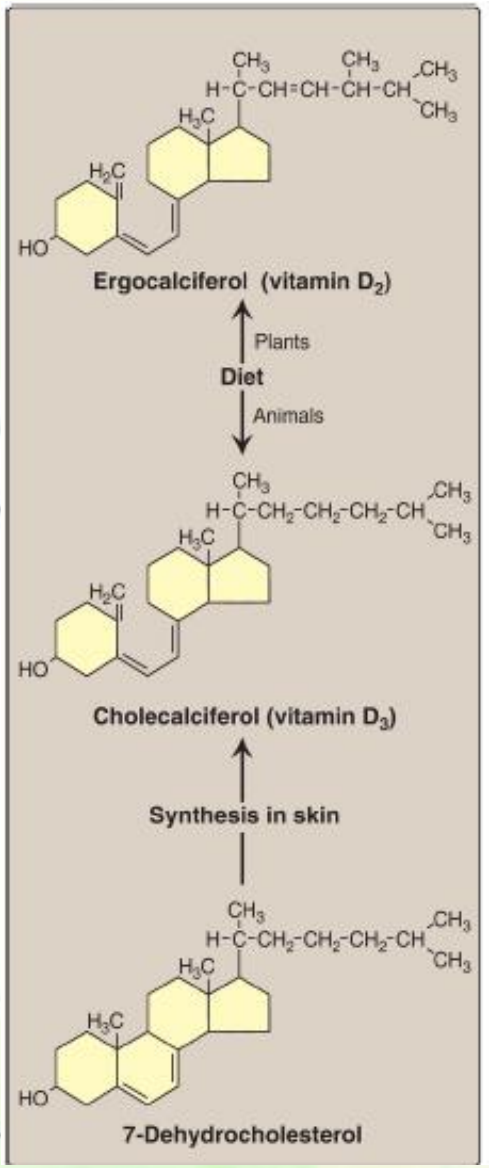
Vitamin D

- It is a sterol with hormone-like functions.
- The active molecule: 1,25-dihydroxycholecalciferol (or calcitriol) binds to intracellular receptor proteins.
- The complex interacts with response elements on the DNA of target cells and selectively regulates gene transcription.



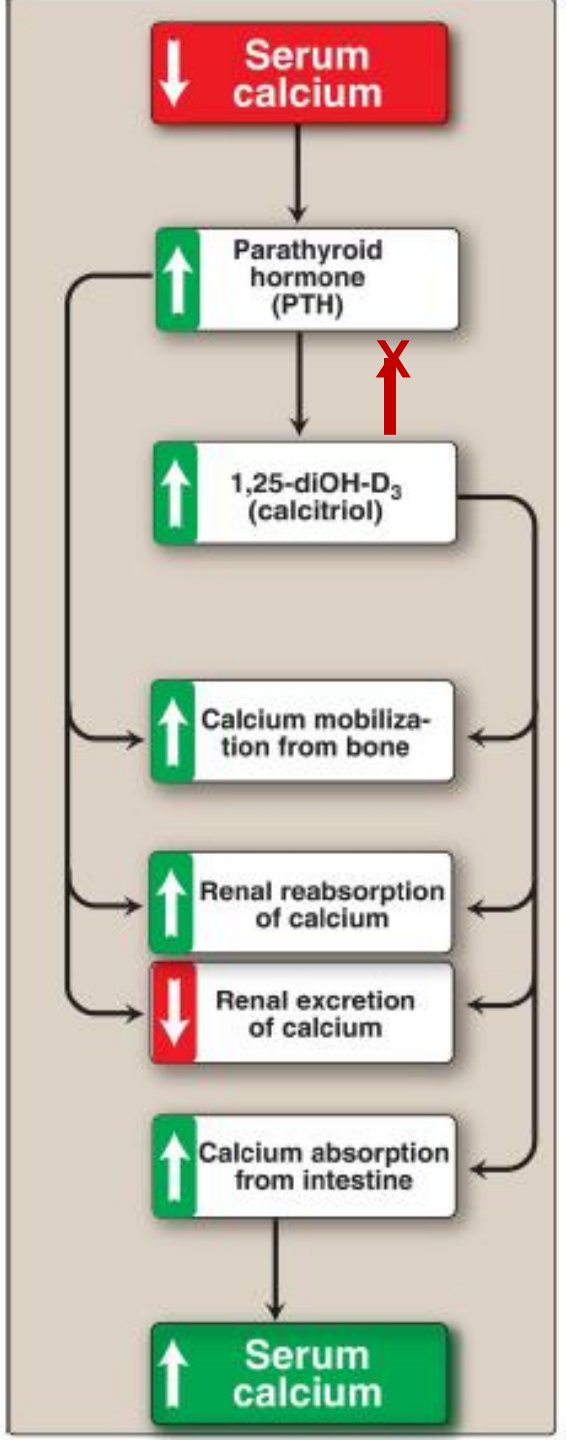
Synthesis of vitamin D





Functions and regulation of vitamin D

- Functions: regulating the serum levels of calcium and phosphorus.
- Formation of calcitriol is regulated by the level of serum phosphate (PO_4^{3-}) and calcium ions (Ca^{2+}).
- 25-Hydroxycholecalciferol 1-hydroxylase activity is increased:
  - Directly by low serum PO_4^{3-}
  - Indirectly by low serum Ca^{2+} (through parathyroid hormone)
- Hypocalcemia caused by insufficient dietary Ca^{2+} results in elevated levels of serum 1,25-diOH-D3.
- 1,25-diOH-D3 inhibits the expression of parathyroid hormone, forming a negative feedback loop.
  - It also inhibits the activity of the 1-hydroxylase.



Distribution and requirement

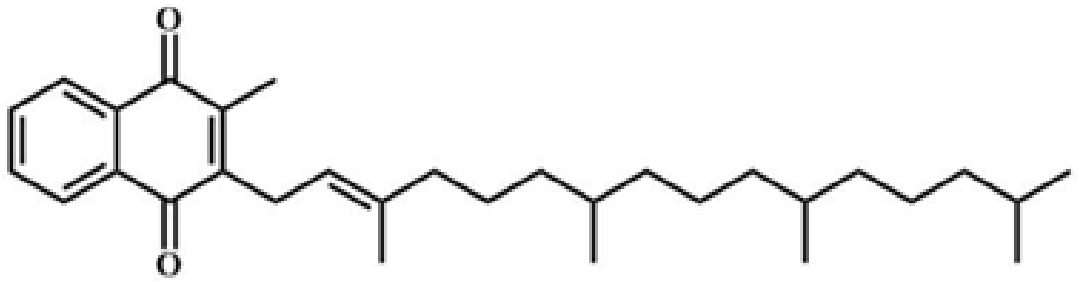
- The RDA for individuals ages 1–70 years is 15 µg/day and 20 µg/day if over age 70 years
  - 1 µg vitamin D = 40 international units (IU)
- Naturally in fatty fish, liver, and egg yolk
- Milk, unless it is artificially fortified, is not a good source
- Because breast milk is a poor source of vitamin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

Toxicity

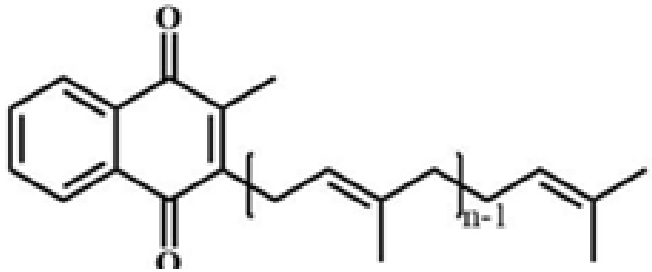
- High doses (100,000 IU for weeks or months) can cause loss of appetite, nausea, thirst, and weakness.
  - The upper limit is 100 µg/day (4,000 IU/day) for individuals ages 9 years or older, with a lower level for those under age 9 years.
- Enhanced Ca^{2+} absorption and bone resorption results in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

Forms of vitamin K

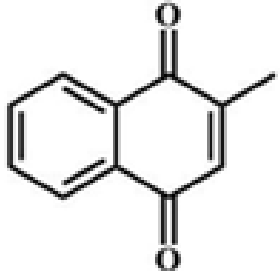
- Vitamin K exists in several active forms:
  - As phylloquinone (or vitamin K1) in plants
  - As menaquinone (or vitamin K2) in intestinal bacteria
  - A synthetic form of vitamin K, menadione, can be converted to K2.



Vitamin K_1
(phylloquinone)



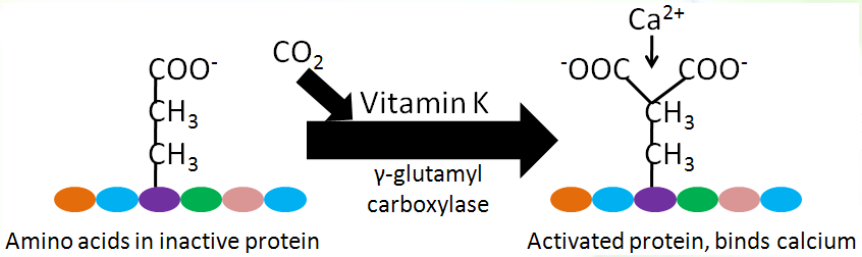
Vitamin K_2
(menaquinone)

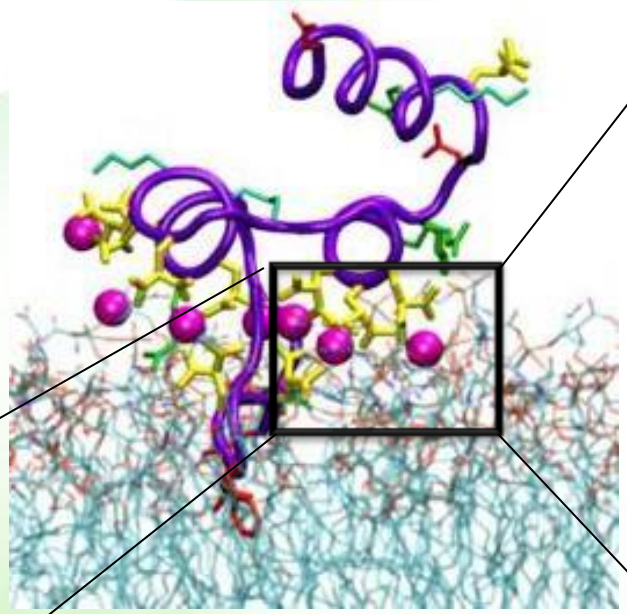


Vitamin K_3
(menadione)

- It is found in cabbage, spinach, egg yolk, and liver.
- There is also synthesis of the vitamin by the gut microbiota.

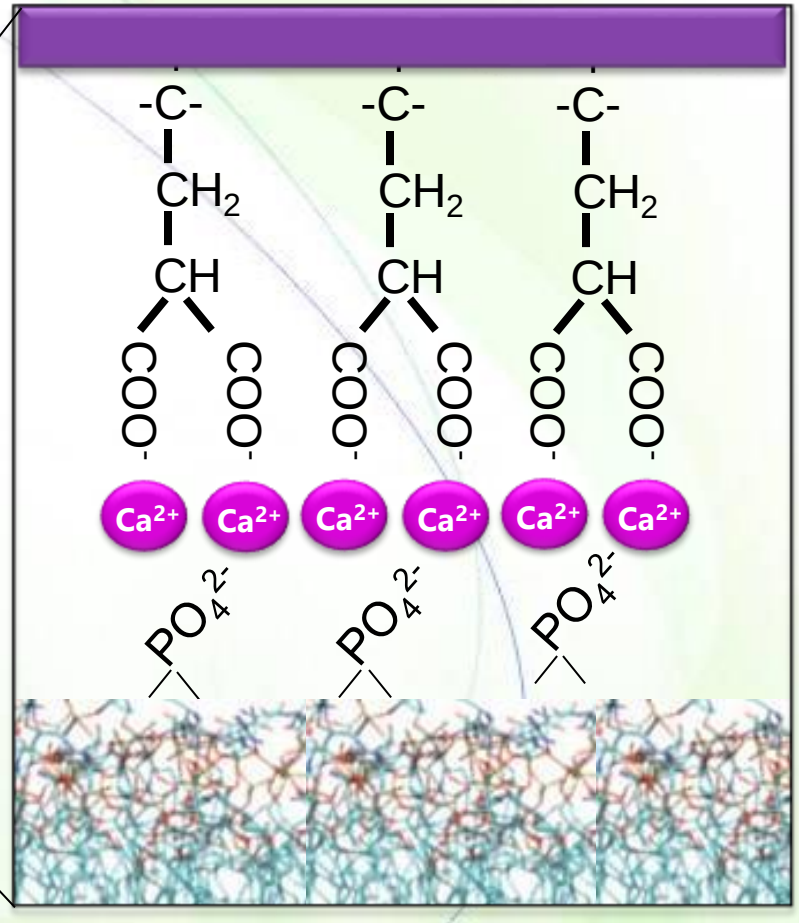
Zoom into the zoom



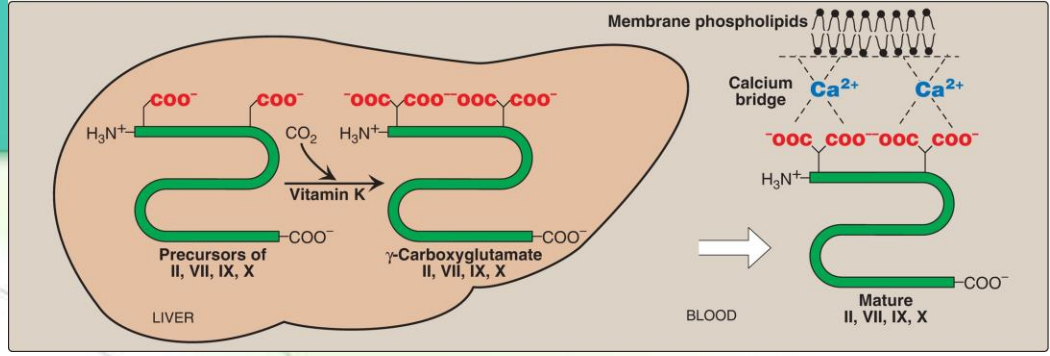


A carboxyglutamate (γ) domain

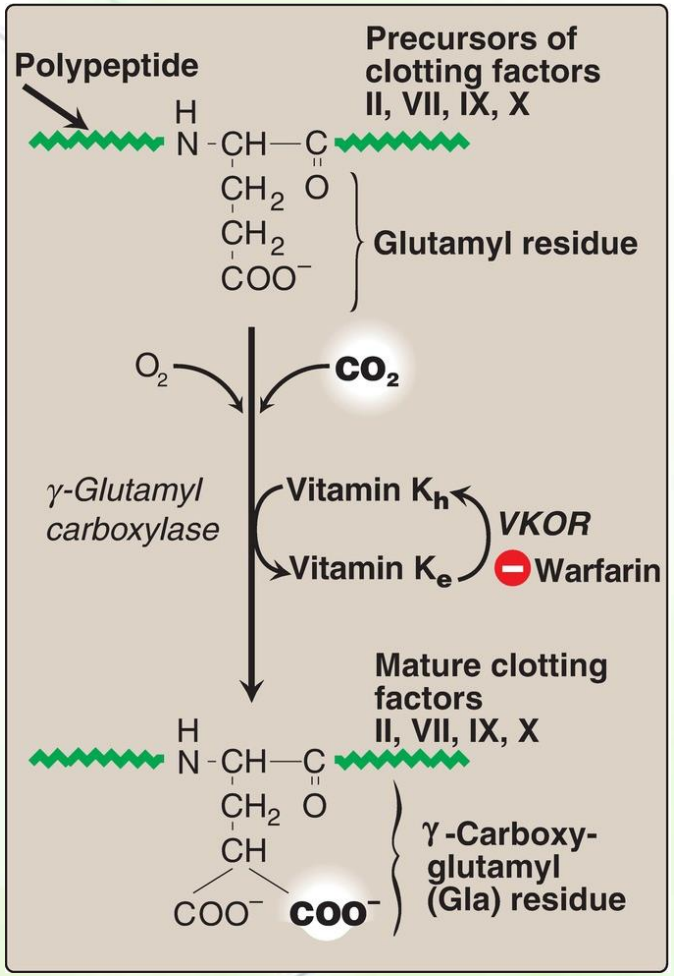
FLγγVRKGNLγRγCVγγTCSYγγAFγALγSSTATDVFWAKYTA



Function of vitamin K



- It serves as a coenzyme in the carboxylation of certain glutamate residues (γ-Carboxyglutamate) of proteins involved in blood clotting.
- γ-Carboxyglutamate allows the attachment of these proteins on the surface of platelets via calcium chelation facilitating their activation and promotion of blood clotting.
- Formation of Gla residues is sensitive to inhibition by warfarin, a synthetic analog of vitamin K that inhibits vitamin K epoxide reductase, the enzyme required to regenerate the functional hydroquinone form of vitamin K.



Clinical indications for vitamin K

- Vitamin K deficiency in adults is unusual but can occur after long antibiotic treatment.
  - Certain cephalosporin antibiotics (for example, cefamandole) cause hypoprothrombinemia, apparently by a warfarin-like mechanism that inhibits vitamin K epoxide reductase.
    - Treatment is usually supplemented with vitamin K.
- Deficiency is mainly restricted in newborns due to:
  - Sterile intestines.
  - Human milk is a poor source of 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 upper limit for the natural form has been set.

Vitamin E

- There are different forms of vitamin K, but α-tocopherol is the most active form.
- The primary function is as an antioxidant.