

III. FAT SOLUBLE VITAMINS

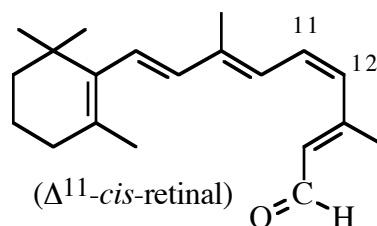
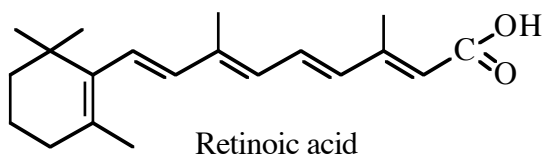
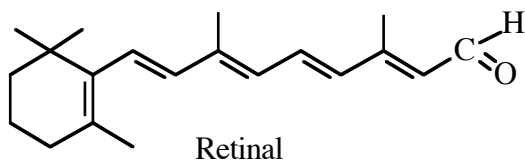
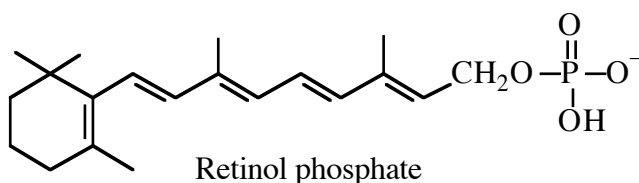
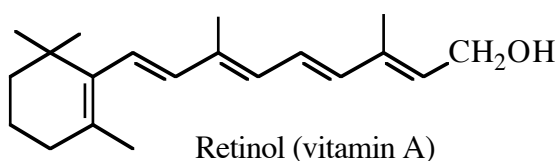
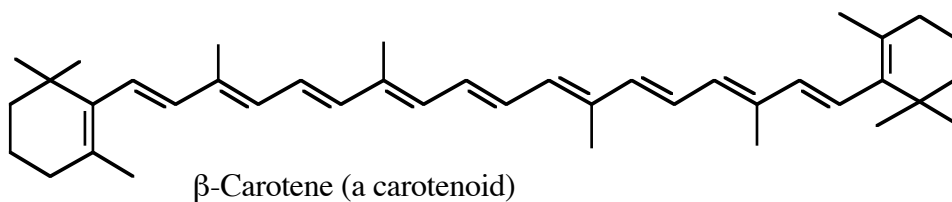
A. Generalities

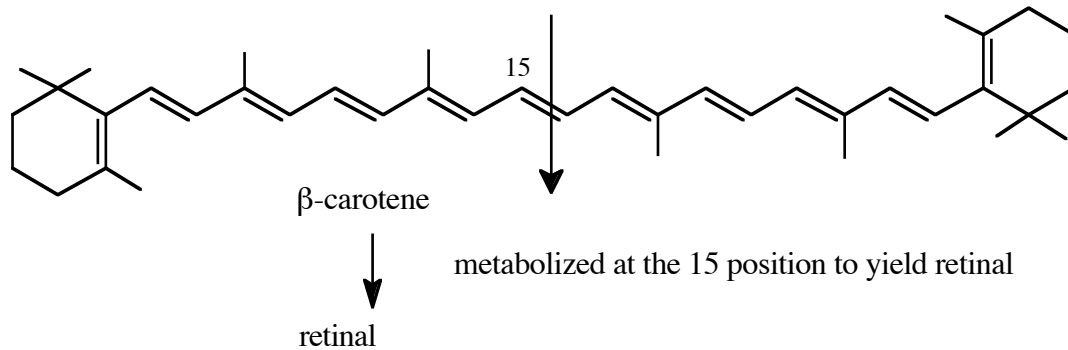
1. Are absorbed in association with lipids -- bile required for absorption; diseases that impair fat absorption can lead to deficiencies.
2. The fat soluble vitamins do not serve as coenzymes but rather act directly or bind to specific receptors in the cell nucleus to influence gene expression.
3. Vitamins A and D are stored in liver and it takes time to bring on a deficiency state.

B. Vitamin A

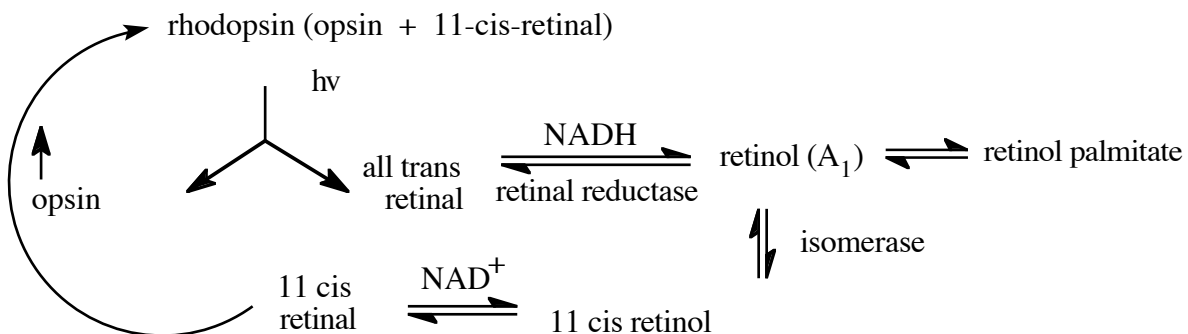
1. Chemistry

- a. A series of compounds are active. Carotenoids are from plants, the retinoids from animals. Of the carotenoids, beta carotene is the most potent but some other plant carotenoids have provitamin A activity. Beta carotene is oxidized to yield (theoretically) 2 moles of retinal. Retinol (mixed esters, especially retinol palmitate) is mostly what is ingested from animal products.





2. **Source** -- plants/carotenoids, animals/retinol.
3. **Transport and storage** specific transport proteins exist for retinoic acid, retinal and retinol. Stored in liver as retinol esters (mostly retinol palmitate)
4. **Deficiency state** –
 - a. Skin- much can be explained by the ability of retinol and retinoic acid to regulate macromolecule synthesis. In the skin absence results in low mucin synthesis and high keratin synthesis (hyperkeratosis). Fissures allow microbe penetration and infection. Vitamin A is known as the “antiinfective vitamin” due to this and the role of the vitamin in immune functioning especially in the activation of T-lymphocytes.
 - b. Iron- vitamin A involved in synthesis of transferrin so that low erythrocyte iron results in anemia.
 - c. Antioxidant/free radical scavenger- carotenoids have this activity
 - d. Cell differentiation: retinoic acid important and low vitamin A associated with an increased risk of various cancers.
 - e. Bone – low intake and high intake increases risks for weak bones.
 - f. Eye- keratinization of the cornea results in xerophthalmia and risk of blindness especially in children.
 - g. Eye- night blindness. 11-cis-retinal binds to opsin to form the low light sensitive rhodopsin. See scheme below.



6. **Requirement** -- adult DV = 5,000 I.U., RDA = 900 μg retinol equivalents (~ 2900 IU) for males and 700ug/d (~ 2300 IU) for females. 1 retinol equivalent = 1 μg retinol = 2 ug

supplement beta carotene or 12 µg dietary β-carotene. 1000 ug retinol is about 3,300 IU; UL=3000ug = ~10,000 IU

7. **Dietary source** – animal products provide retinol esters, plants provide carotenoids. The richest sources are animal livers and fish oils. Eggs and fortified dairy products are also important.
8. **Stability** -- O₂ labile, as are most unsaturated fats.
9. **Use**
 - a. Deficiency state.
 - b. skin-
 - a. Acne -- topically as retinoic acid. Systemically as 13-cis retinoic acid (isotretinoin) Accutane® Roche. Attention: these retinoids are strong teratogens.
 - b. Psoriasis – etretinate (Tegison®); acitretin (Soriatane®)
 - c. Cancer -- Vitamin A deficiencies associated with increased sensitivity to carcinogens and increased tumor incidence but prospective studies with supplements have not shown consistent benefit. There is an association of low carotene intake and increased risk of lung cancer in smokers. However, supplementation of beta carotene to smokers gave an increased risk of lung cancer!
 - d. Low vitamin A intake is associated with more severe infectious diseases including HIV. The infectious process lowers vitamin A also. Retinol being evaluated by the WHO in some developing countries to decrease mortality in children due to measles and other infectious diseases. One study showed that severe measles in the USA was associated with low retinol levels.
 - e) Fat soluble free radical scavenger as carotenoids.
 - f) lycopene a carotenoid (diets rich in tomatoes) with no vitamin A activity seems to have benefit in preventing prostate cancer. Doses of 6-30mg used.
 - g) luteine a carotenoid (diets rich in broccoli, spinach, and kale) with no vitamin A activity seems to have benefit in preventing macular degeneration. Supplements may help prevent progression. Doses of 7-20mg used.
10. **Toxicity**
 - a. Hypercarotenosis -- eat too many carrots -- turn yellow, but no harm done.
 - b. Hypervitaminosis A -- characterized by hydrocephalus, vomiting, hypercalcemia and brittle bones, fatigue, malaise, joint pain, headaches, rough skin, swellings on the extremities, papilledema caused by increased production of spinal fluid (symptoms of brain tumor), hepatotoxicity.

Can be precipitated by chronic ingestion of 25,000 to 50,000 I.U./day

Note: cod liver oil has about 5,00 IU/5ml. Liver has about 30,000 IU/3 oz.

- c. Teratogenic? - recent evidence says yes in doses > 10,000 I.U./d.

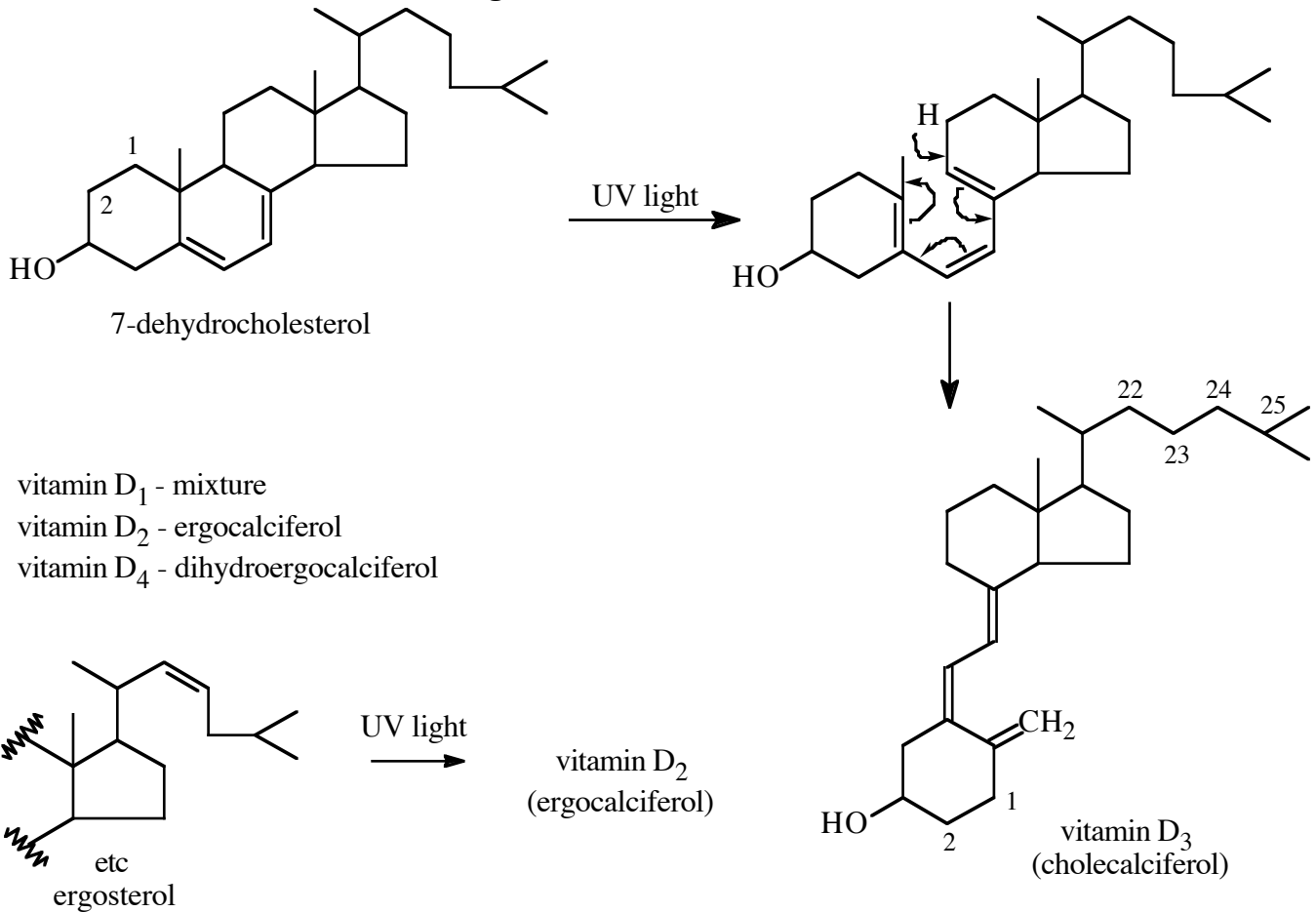
Note: Watch out for polar bear liver -- has 20,000 to 30,000 I.U./g.

- d. Risk for fractures – intakes of retinol from all diet and supplements over about 10,000 IU is associated with increased risk for fractures in men and women. Avoid single supplements and excess dietary intake unless there is a compelling reason to do so. Carotenoids are OK.

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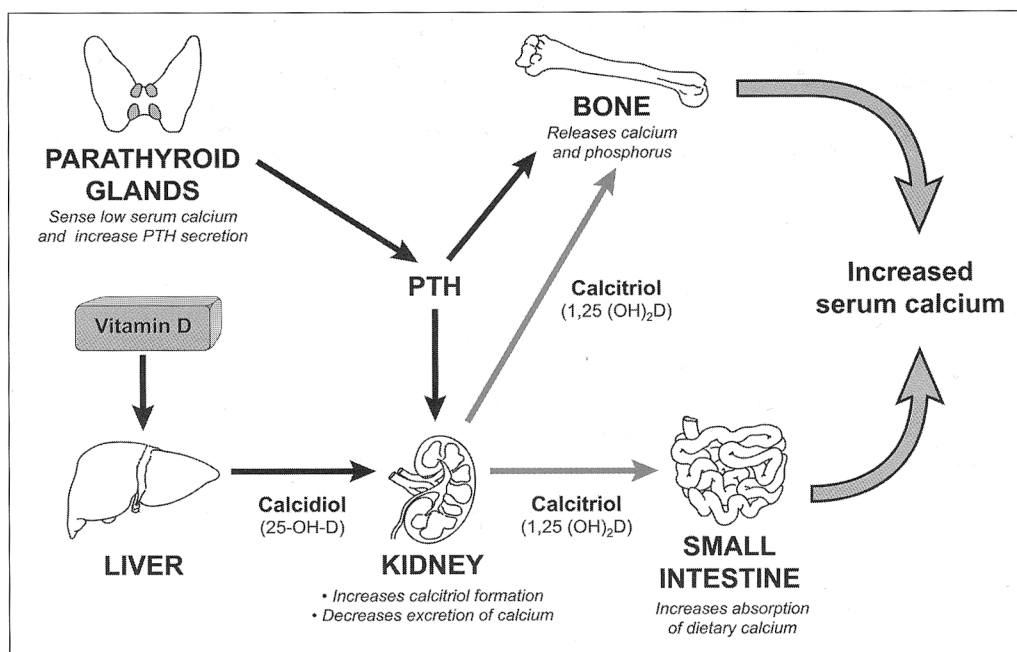
C. Vitamin D

1. Structures D-1 through D-4

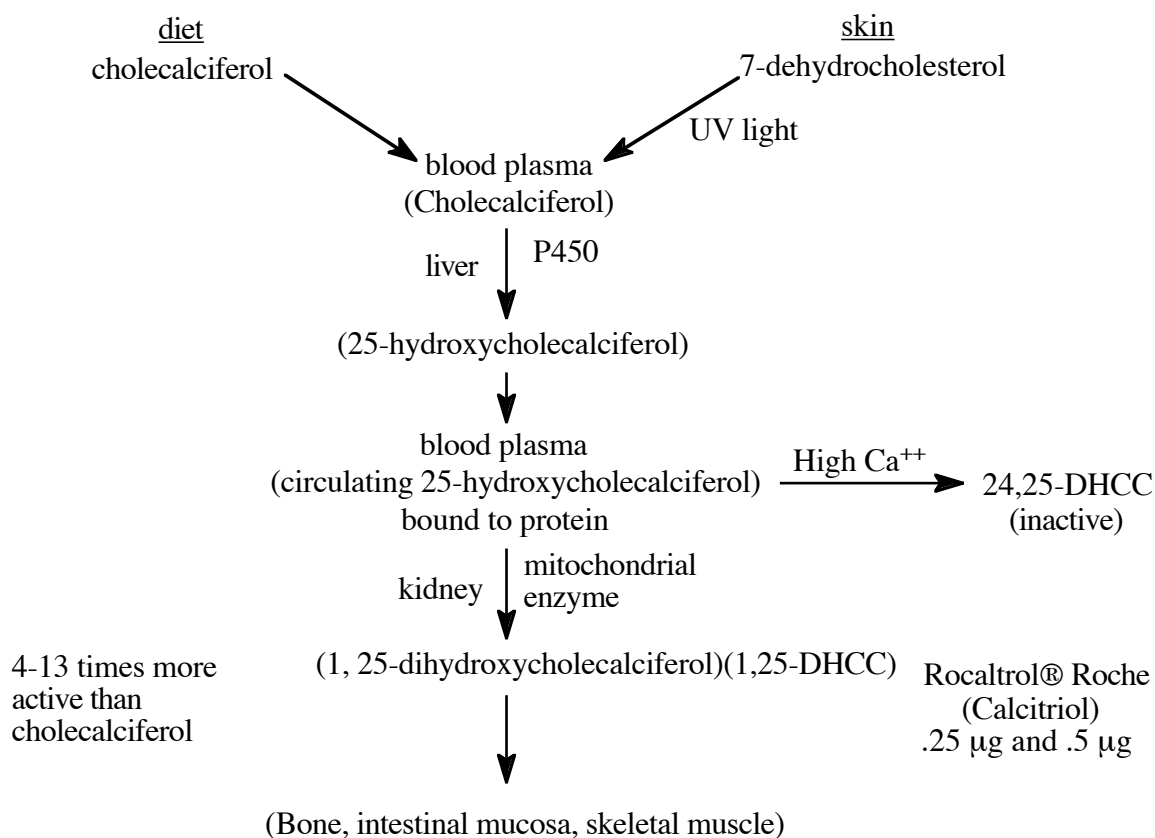


2. Deficiency state -- rickets, osteomalacia.

3. Function -- Vitamin D as 1,25 DHCC is necessary for signaling gene transcription of calcium transporters that are involved in absorption of Ca through the intestinal mucosa. Vitamin D as 1,25 DHCC is also involved in cell regulation and differentiation.



4. Metabolites --



5. **Toxicity** -- avoid high doses, especially in infants; 400 units/day = potentially toxic for infant, 150,000 units/day = potentially toxic for adult, calcification of soft tissues (lung, kidney).

6. **Requirements** -- DV = 400 I.U.; AI = 15 µg (~600 IU) cholecalciferol. UL=2000 IU
7. **Source** -- fish liver, fish products, sunshine, eggs (in D supplemented hens), liver, milk (fortified). Cod liver oil has about 400 IU/5ml.
8. At risk for deficiency
 - i. Infants kept out of sun
 - ii. Elderly with minimal sun
 - iii. Dark skin with minimal sun
 - iv. Religions that cover the whole body.
 - v. Fat malabsorption
 - vi. Inflammatory bowel diseases
 - vii. Kidney failure
 - viii. Seizure disorders treated with anticonvulsants which increase D elimination

9. **Use**

- deficiency state
- hypoparathyroidism to keep calcium serum levels adequate
- osteomalacia and osteoporosis. Use 1,25 DHCC in renal failure.
- There is now strong evidence that vitamin D supplements and calcium help prevent fractures in postmenopausal women. (20-30% decrease).
Most studies used 700-900 IU per day.
- There is strong interest in a potential role of vitamin D and calcitriol in the prevention of several cancers, especially colon, breast and prostate.
There is an inverse association of D & Ca intake and risk for colon cancer.
- MS risk. Seems to be an inverse relationship of intake and risk.

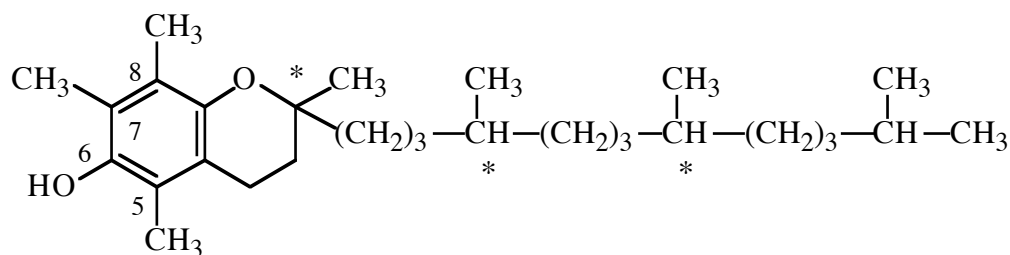
Calcitriol (Rocaltrol® Roche and generic products) -- 1,25-dihydroxy D₃ -- the "active" metabolite. Available in capsules and injection.

Paricalcitol (Zemlar®)–

Modification of 1,25 DHCC used PO for hyperparathyroidism associated with renal failure. 1µg 3 times per week.

D. Vitamin E

1. Structure



There are 8 possible stereoisomers. "Natural" vitamin E is RRR- α -tocopherol. RBC levels of RRR are higher than with an equal dose of the racemate.

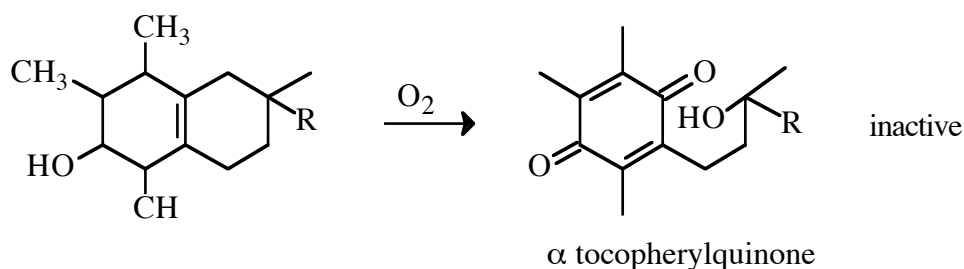
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|--------------------|----------------------------------|-----------------|-----------|
| 2. <u>Activity</u> | d- α -tocopherol | 1 mg = 1.5 I.U. | |
| | dl- α -tocopherol | 1 mg = 1.1 I.U. | synthetic |
| | dl- α -tocopherol acetate | 1 mg = 1.0 I.U. | synthetic |

Other tocopherols are active:

β = 7-demethyl	1 mg = 0.1 I.U.
α = 5-demethyl	1 mg = 0.1 I.U.
δ = 5,7-demethyl	1 mg = 0.1 I.U. (present in large amounts of corn)

3. Stability

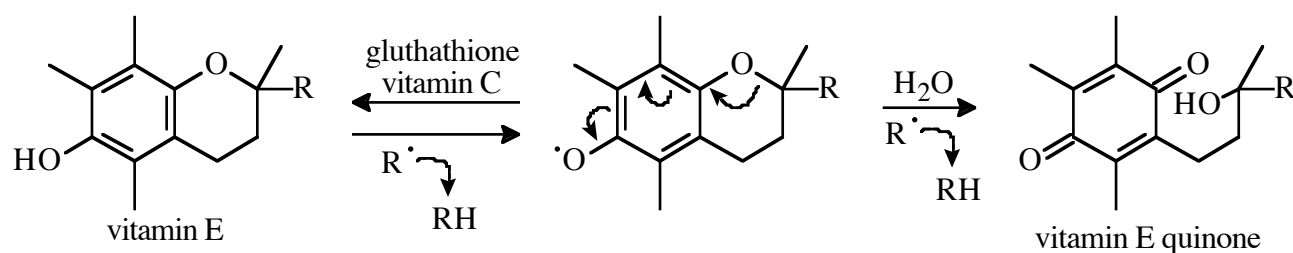
Much is lost during processing and cooking. White, bleached flour has almost all E destroyed.



Iron catalyzes the oxidation.

3. Properties -- Good fat soluble, antioxidant, good chain breaking free radical scavenger.

Vitamin E as a free radical scavenger



4. **Effects—**

- Has mild effect in decreasing platelet aggregation due to an effect on decreasing the activity of cyclooxygenase (therefore decreased conversion of arachadonic acid to thromboxane).
- Decreases LDL oxidation
- Decrease smooth muscle proliferation
- Preserves endothelial cell function
- Decreases monocyte reactive oxygen species (ROS)
- Effects transcriptional regulation of some genes

5. **Distribution** -- Almost ubiquitous; rich sources are seed germ oils, green vegetables, whole grain cereals; margarine supplies much of our intake in the U.S.

6. **Deficiency state**

Animal Species	Syndrome
Rat (male)	sterility, liver necrosis
Rat (female)	fetal resorption, liver
Rabbit	muscular dystrophy, myocardial degeneration
Dog and Guinea Pig	Myocardial degeneration
Primate	Macrocytic anemia, muscular dystrophy

Man

A dietary deficiency of E is rare. A deficiency state was seen in some premature infants (stores of E are low at birth due to poor placental transport where edema and hemolytic anemia has been observed when the infants were fed a formula low in E and high in polyunsaturated fatty acid). In diseases resulting in malabsorption of fats, a neurological impairment observed has responded to vitamin E.

7. **Requirement** -- DV = 30 I.U. new RDA is 15mg (~22 IU of natural or 33 IU of synthetic). UL = 1000mg (~1500 IU natural or ~2200 of synthetic)
8. **Biological function of E** -- Acts as a general fat soluble biological antioxidant to prevent free radical oxidation of lipids and hence essential membrane destruction. More on this later.
9. **Uses** -- The claims for benefit of supplements of vitamin E are numerous and include increased virility, increased athletic performance, and help for diabetes, heart disease,

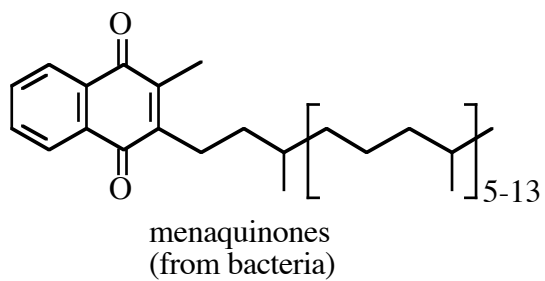
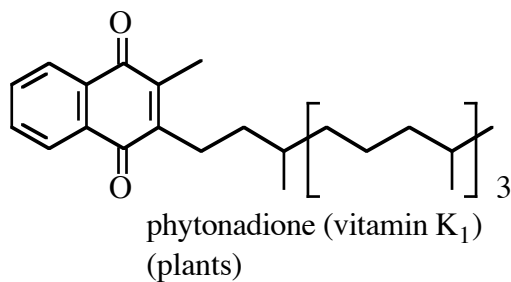
dementia, cancer and aging. Retrospective studies have showed that daily use of vitamin E supplements in doses of > 100 IU have been associated with a decreased risk for coronary heart disease in both men and women (*New Eng. J. Med.* **328**:1450, 1993 and **328**:1444, 1993). Prospective studies, however, in humans have not confirmed this although most have been secondary prevention studies in populations already at high risk. Dietary intake studies and retrospective studies may be confounded.

- a. Intermittent claudication -- Long-term treatment with 400 I.U./day; vitamin E has been reported to be of benefit in two older clinical studies.
 - b. Parkinson's disease – inverse risk relationship with increased dietary intake; observational studies
 - c. Coronary and vascular disease – no effect but studies mostly involved high risk populations [Arch Intern Med.](#) 2004 Jul 26;164(14):1552-6..
 - d. All cause mortality – A small **increase** at doses over 400IU. Most studies were in high risk populations, however. A small decrease in mortality in doses <400 IU ([Ann Intern Med.](#) 2005 Jan 4;142(1):140.)
 - e. Tardive dyskinesia – some promise for benefit of supplements [Ann Clin Psychiatry.](#) 1998 Sep;10(3):101-5.
 - f. Pre-eclampsia – some promise in prevention with supplements
 - g. Athletic performance -- no benefit in competitive swimmers.
 - h. Nocturnal leg cramps -- Evidence is suggestive of benefit, but careful evaluation has yet to be done.
 - i. Increased sexual performance and function -- Sorry, no help here!
 - j. Retrolental fibroplasia and Brochopulmonary dyspasia. Eye and lung damage in premature infants on oxygen; as an antioxidant, E seems to offer some protection, but deaths have occurred. These deaths occurred in Wash. State and were associated with IV admin. of tocopherol. This form is no longer available and MVI Pediatric (Astra) is used as a source of IV Vitamin E for premature infants.
 - k. PMS -- one controlled study showed benefit. Controversial.
 - l. Dysmenorrhea – 2 studies showed benefit in teens.
 - m. Alzheimers Disease -- high doses (2000 IU/d) showed some benefit in decreasing progression but not in prevention.
 - n. Dementia – in >73 years old study population, long term use associated with decreased risk (but not for Alzheimer's)
 - o. Cancer – supplement use gave decreased risk for prostate cancer in smokers.
10. **Toxicity** --Tocopherols are generally considered non-toxic. Various rare diverse adverse effects have been reported. Exacerbated bleeding when given together with coumarin

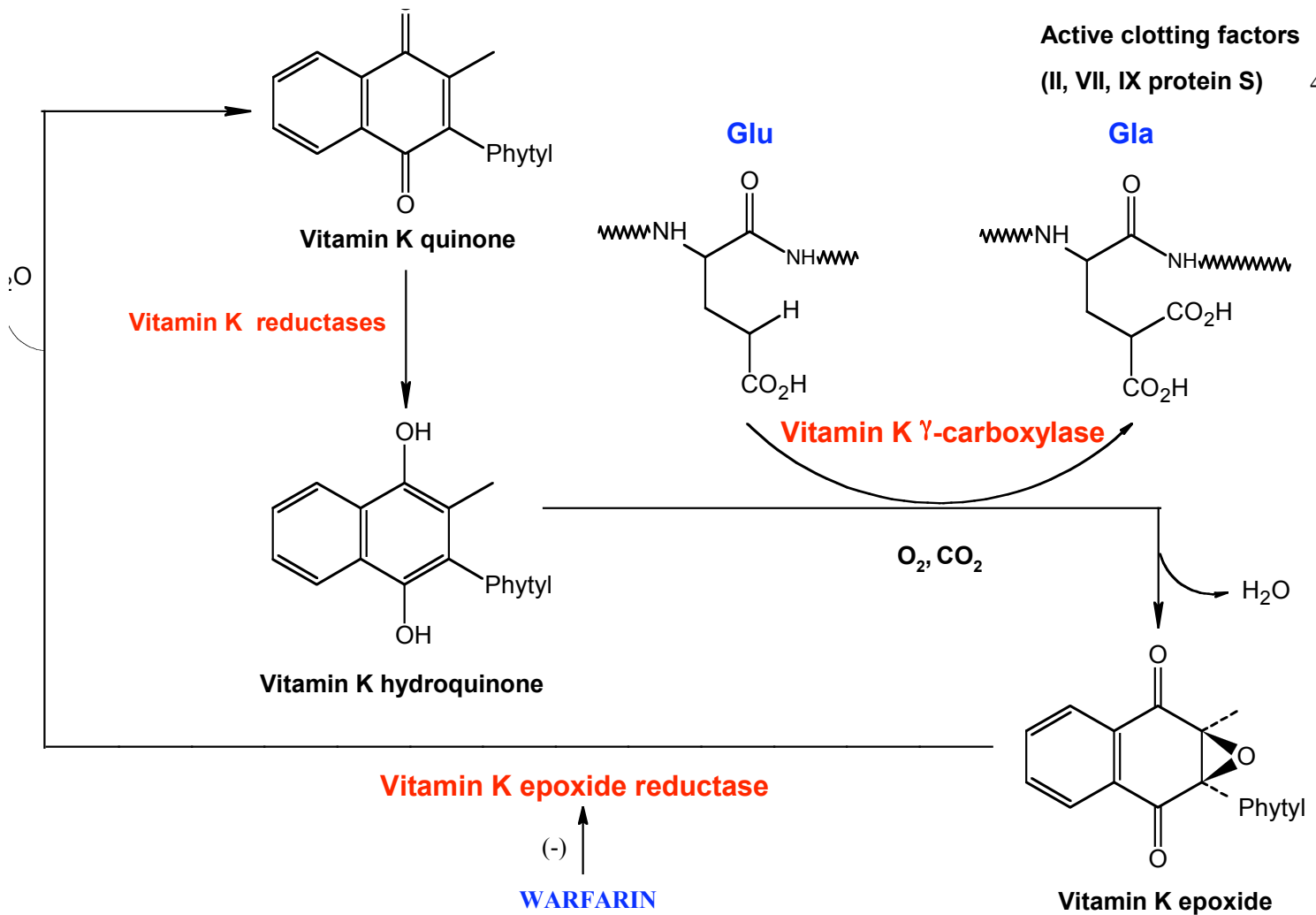
anticoagulants is the most significant drug interaction involving Vitamin E. Doses over the UL have this risk.

E. Vitamin K -- Group of naphthoquinones having antihemorrhagic activity.

1. Chemistry



- 2. Function** -- Necessary for carboxylation of γ glutamyl residues on precursor proteins
 → activation → blood coagulation.
 Also γ carboxylation of osteocalcin in bone.



Vitamin K scheme for γ carboxylation of glutamyl residues on precursor clotting proteins

3. **Deficiency** -- Deficiency state can come on fast because K is not stored. Long term antibiotic therapy may increase risk of deficiency because ~ 50% comes from intestinal bacteria.
5. **Use** –
 - a. Coagulation - Water soluble derivatives used for IV and where absorption is impaired. For an anticoagulant overdose, use K1. K1 is used routinely at birth IM to prevent neonatal hemorrhage.
 - b. Bone – This is new. Gamma carboxylation of osteocalcin is enhanced with improved bone deposition. Use of 25mg/d for 2 years decreased hip fractures in an older population.
5. **Source** -- Spinach, cabbage, tomatoes, other green vegetables.
6. **Dose** – 80ug is DV. This may be too low for optimal activities. No UL.
7. **Toxicity**– some allergic reactions IV but not IM or PO. Otherwise nothing special.

IV. OXIDATIVE STRESS AND PROTECTIVE MECHANISMS INVOLVING VITAMINS

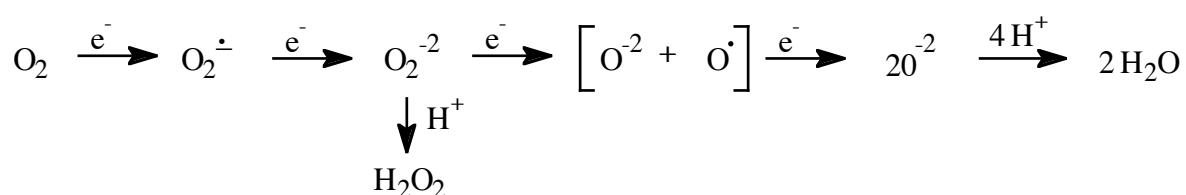
Reactive oxygen species that result in tissue damage (drugs, pesticides, pollutants can cause tissue damage via oxidative metabolism).

Importance - inflammation, carcinogenesis, hemolysis, atherosclerosis, arthritis, aging, drug adverse effects.

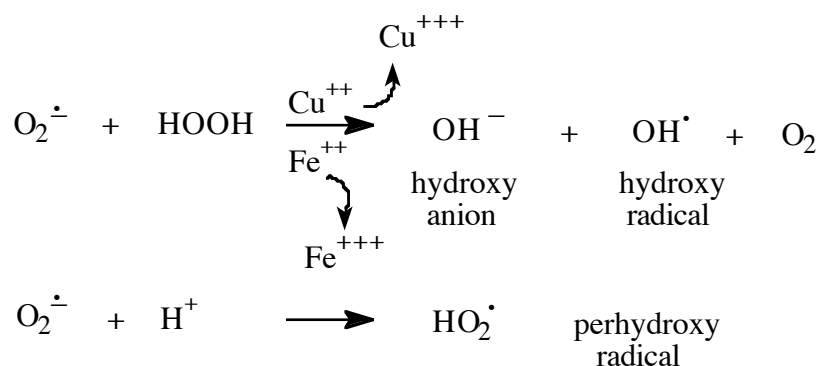
Reactive O₂ species causing damage:

- Complete reduction of O₂ $O_2 + 4H^+ + 4e^- \longrightarrow 2H_2O$

but this goes in 1 electron steps

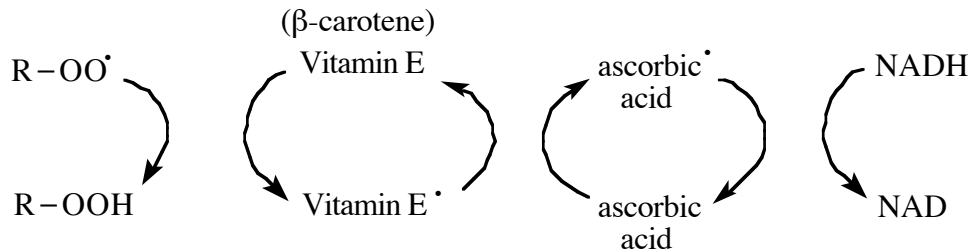


- Reactive species



- Origin of e⁻ - oxidation of hydroquinones, flavins, thiols, drugs, mitochondrial respiration, microsomal reactions, UV light radiation, etc.

2. **Superoxide dismutase:** $2 \text{ O}_2^{\cdot -} \xrightarrow{\text{H}^+} \text{H}_2\text{O}_2 + \text{O}_2$
3. **Catalase:** $2 \text{ H}_2\text{O}_2 \longrightarrow 2 \text{ H}_2\text{O} + \text{O}_2$
4. **Vitamins A, β -carotene, C, and E and selenium**



Issues:

Should supplements of antioxidant vitamins be routinely recommended?

Is there evidence that antioxidant use has long term benefit?

Are there adverse consequences of taking antioxidant supplements?

What doses should be used if use is deemed safe and worthwhile?

In my opinion, the definitive answers to these questions are not yet available.

V. MULTIVITAMINS

A. Need?

Do we need to supplement diets with multivitamins? Many say no; others say maybe in certain circumstances, some say yes.

Cases where multivitamin supplements are clearly worthwhile:

Inadequate intake -- alcoholics, poor, elderly, dieters, poor diet

Poor absorption -- elderly, GI disorders, cystic fibrosis, diarrhea

Increased needs -- pregnancy, lactation, infants, smokers, injury, trauma, surgery, infection

Iatrogenic Vitamin Deficiencies -- oral contraceptives, long term antibiotic use, isoniazid, cholestyramine.

B. Available multivitamin preparations -- product selection guidelines