

Study questions from last week:

- 1) What patient history, laboratory findings, or physical exam may make you suspect a vitamin B12 deficiency?
 - a. Atrophic gastritis→especially those pts >50yrs
 - b. Pt w/ resection of terminal ileum
 - c. PE finding
 - i. Neuropathy-tingling (early stage), complete loss of sensation (in later stages)
 - ii. Fatigue
 - d. labs
 - i. CBC→macrocytic anemia
 - e. Inflammatory mediators
 - i. Homocysteine, MMA (methyl malonic acid), and maybe CRP
 - ii. Non of these labs are infallible

 - 2) The federal government mandates fortification of white flour with 140 mcg / 100 grams of flour.
 - a. Is this necessary?
 - i. Helps prevent neural tube defects
 - ii. We don't eat foods that supply folic acid in a high enough amount
 1. Public health has not been able to get people to eat in ways that would ↑ folic acid. The movie "Supersize me" talks about public health's budget to improve America's diet vs the fast food industry's budget to push unhealthy diets
 - b. Is this Sufficient?
 - i. 100g of fortified flour would not be enough to prevent neural tube defects (need 400mcg→just under 1lb of white flower)
 - ii. There are obviously better ways to ↑ folic acid than via white flour

 - 3) What are the advantages to the use of niacin to treat high cholesterol? The disadvantages?
 - a. See last week

 - 4) Why is the upper limit of vitamin B6 supplementation set at 100 mg per day? Would you feel comfortable recommending more than this to a patient?
 - a. Upper limit =100mg→higher doses can cause neural toxicity sx's
 - b. Research for therapeutic doses of B6 is mostly short-term use
 - i. If you decide to use B6 in doses >100mg for long-term
 1. Warn pts that this medication has a potential side affect of numbness/tingling in fingers and toes (good to always warn pts of side affects, even if rare)
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Diet and nutrient therapy: week four handout

Vitamin C

Biochemistry: Involved in the manufacture of collagen. Water-soluble antioxidant. Protects LDL against oxidation (early event in the pathophysiology of atherosclerosis).

Deficiency= scurvy

1. pathophysiology
 - a. vit c involved in the cross linking of collagen→not enough vit C→weak connective tissue
2. gum deformation
3. bone deformation

Indications:

- 1) **Common cold and other viral infections:** Oral doses of 500 mg, 3 times per day or more, up to bowel tolerance, may accelerate recovery. Some individuals with mononucleosis have reportedly tolerated up to 200 g/day during the acute stages of the illness. As their condition improved, the amount of vitamin C tolerated decreased. Intravenous administration of vitamin C in doses up to 75 g may be effective for acute viral infections (e.g., mononucleosis or hepatitis). There are numerous double-blind trials for the common cold, with most showing a reduction in severity, but no reduction in incidence. Evidence with respect to other viral illnesses is mostly anecdotal. One of the most prominent negative trials found a 20% reduction in symptom duration, but this was not statistically significant. Slight preventive effect, too.

Vit C has been shown to improve neutrophil activity, especially in athletes. Marathon runners given Vit C after a race are less likely to get an infxn. Not clear if vit C improves immune function in non-athletes.

mechanism of action

- Scavenging free radicals

2 clear patterns from research

- Must Vit C start early in dz
 - Shortens duration (20-30%)
- **PMID: 1578094;** Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. J Am Coll Nutr. 1992 Apr;11(2):172-6.
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- **PMID: 9059230**; Vitamin C intake and susceptibility to the common cold. *Br J Nutr.* 1997 Jan;77(1):59-72.
- **PMID: 12201356**; *Adv Ther.* 2002 May-Jun;19(3):151-9.
- **PMID: 463806**; *Am J Clin Nutr.* 1979 Aug;32(8):1686-90

2) **Atherosclerosis:** Vitamin C, at a dose of 500 mg, 3 times per day for 2-6 months, induced regression of femoral atherosclerosis in 6 of 10 patients (controlled, unblinded trial). Vitamin C has been found to inhibit platelet aggregation, increase HDL cholesterol, and prevent endothelial dysfunction in humans. In one study, vitamin C at 500 mg tid helped to prevent restenosis (restenosis=renarrowing after angioplasty→80% of pts will have restenosis after 5yrs of angioplasty procedure) after angioplasty. Similar dose has been shown to improve arterial insufficiency before advent of angioplasty.

- **PMID: 12893026**; Role of ascorbic acid in the modulation of inhibition of platelet aggregation by polymorphonuclear leukocytes. *Thromb Res.* 2003 May 1;110(2-3):117-26.
- **PMID: 8960592**; Possible prevention of postangioplasty restenosis by ascorbic acid. *Am J Cardiol.* 1996 Dec 1;78(11):1284-6.

3) **Hypertension:** At a dose of 500 mg/day, vitamin C produced significant reductions in systolic blood pressure in elderly individuals (double-blind trials).* Reduction in diastolic blood pressure was seen as well, but it did not reach statistical significance.

Physiology lesson: Loss of compliance in the aorta can drive up systolic BP. Dr B learned that A normal systolic pressure is 120plus your age minus 20→this is not true. If your systolic BP is above 140 (maybe even 130)→independent risk factor for stroke and kidney dz. Wide pulse split (40-50) → person may have atherosclerosis. Also when systolic is up and diastolic is not up think about using Vit C. When both systolic and diastolic is up think about minerals (potassium) and diet.

- **PMID: 15133406**; The natural treatment of hypertension. *J Clin Hypertens (Greenwich).* 2004 May;6(5):242-8.
- **PMID: 15087291**; Protective effects of ascorbic acid on arterial hemodynamics during acute hyperglycemia. *Am J Physiol Heart Circ Physiol.* 2004 Sep;287(3):H1262-8. Epub 2004 Apr 15.
- **PMID: 15023611**; Effects of vitamin C and grape-seed polyphenols on blood pressure in treated hypertensive individuals: results of a randomised double blind, placebo-controlled trial. *Asia Pac J Clin Nutr.* 2003;12 Suppl:S18.
- **PMID: 10636373**; Treatment of hypertension with ascorbic acid. *Lancet.* 1999 Dec 11;354(9195):2048-9.

4) **Asthma:** Some, but not all, double-blind studies have shown a reduction in symptoms and in airway reactivity with 500-1,000 mg/day. Epidemiological studies indicate that increased vitamin C intake is associated with lower risk of asthma. This is especially effective if symptoms are related to pollution (mexico city has most polluted air). Children w/ asthma in mexico city: Vit C helped on the worst days of air quality but little affect on the best days of air quality. Vit C also helpful in kids w/ exercise induced asthma.

- **PMID: 12587963**; Dietary vitamin C intake is inversely related to cough and wheeze in young smokers. *Respir Med.* 2003 Feb;97(2):134-42.
 - **PMID: 7879729**; Asthma, inhaled oxidants, and dietary antioxidants. *Am J Clin Nutr.* 1995 Mar;61(3 Suppl):625S-630S.
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- **PMID: 12204869**; Am J Respir Crit Care Med. 2002 Sep 1;166(5):703-9

- 5) **Degenerative disc disease:** One orthopedic surgeon has published a case series concluding that supplementation with 1-3 g/day of vitamin C greatly reduced the need for spinal-disc surgery in his patients.* Dr B hasn't used Vit-C for this dz
- 6) **Cancer:** In an uncontrolled trial, 10 g/day of vitamin C increased the survival time of terminal cancer patients by more than 5-fold. This uncontrolled trial is criticized because they were comparing pts to historical controls from the 1970s→flaw=the care was different in the past. Two double-blind trials (one by Mayo clinic) failed to confirm these results; however, these trials have been criticized because of methodological flaws (urine of placebo group had vit C present & they looked at dz progression, not survival time. Looking at tumor shrinkage/dz progression is more appropriate for assessing chemo Tx not Vit C Tx). The role of vitamin C in cancer therapy remains controversial.*

Linus Pauling came up w/ this use. Using anti-oxidants w/ chemo remains controversial. Lots of people are using high dose IV vit C→may be a pro-oxidant therapy which has been shown to cause necrosis of CA cells (pro-oxidant Tx has worked w/ kidney CA's, but these are also the most likely CA's to spontaneously remit). Dr B thinks the research is shaky for IV vit C and has not seen good outcomes in clinics he's observed this Tx used in.

- **PMID: 1068480**; Proc Natl Acad Sci U S A. 1976 Oct;73(10):3685-9.
- **PMID: 384241**; N Engl J Med. 1979 Sep 27;301(13):687-90
- **PMID: 3880867**; N Engl J Med. 1985 Jan 17;312(3):137-41

- 7) **Glaucoma:** High doses of vitamin C (10-35 g/day in divided doses) reduced intraocular pressure in patients with glaucoma (uncontrolled trials). Lower doses (such as 500 mg, 2 times per day) were of minimal benefit. Chronic simple glaucoma responded better than did secondary glaucoma or hemorrhagic glaucoma.
- **PMID: 11464071**; Involvement of oxygen free radicals in experimental retinal ischemia and the selective vulnerability of retinal damage. Ophthalmic Res. 2001 Jul-Aug;33(4):196-202.
 - **PMID: 10580784**; Serum ascorbic acid and other correlates of self-reported cataract among older Americans. J Clin Epidemiol. 1999 Dec;52(12):1207-11.
- 8) **Lead accumulation:** supplementation for one week with 1000 mg of vitamin C reduced blood lead levels in smokers by over 80%. 200 mg had no effect (J Am Coll Nutr. 1999 Apr;18(2):166-70). Lead of cig smoke dissolves in saliva and is absorbed via GI (not via lungs)→ vit C may prevent this GI absorption.
- **PMID: 10386552**; Relationship of ascorbic acid to blood lead levels. JAMA. 1999 Jun 23-30;281(24):2289-93.
 - **PMID: 10204833**; The effect of ascorbic acid supplementation on the blood lead levels of smokers. J Am Coll Nutr. 1999 Apr;18(2):166-70.
- 9) **Allergies:** Vitamin C has been used empirically by many physicians to reduce symptoms of nasal allergy. Only published controlled trial showed no benefit to vitamin C. Basic science research has shown an antihistamine effect of vitamin C. Vit C and quercitin can prevent the degranulation of mast cells in test tubes but at levels that are not possible to achieve in human serum.
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- **PMID: 7076989**; The effect of ascorbic acid on cutaneous and nasal response to histamine and allergen. *J Allergy Clin Immunol.* 1982 Jun;69(6):484-8.

10) **Reflex sympathetic dystrophy:** 500 mg daily of vitamin C reduced incidence of RSD by 15% when started immediately post-wrist fracture. RSD follows a nerve pattern and can cause changes in skin. Can occur about 6 weeks after a traumatic event (esp wrist Fx) and causes flushing and cutaneous sx's.

- **PMID: 10636366**; Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet.* 1999 Dec 11;354(9195):2025-8.
- **PMID: 1578094**; Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. *J Am Coll Nutr.* 1992 Apr;11(2):172-6.

11) **Osteogenesis imperfecta:** Vitamin C supplementation (20-50 mg/kg/day or 1,000 mg/day) for up to 3.5 years reduced the development of new fractures by more than 70% (2 uncontrolled trials).*

12) **“Compensation” for the result of a universal human genetic defect, absence of L-gulonolactone oxidase:** Theoretically, full compensation (“bowel tolerance doses”) for this problem will improve multiple parameters of human health. Original research on Vit C was done on the finding that most mammals will ↑ vit C production in presence of infxn and CA. Guinea pigs and humans are the only mammals that cannot make endogenous Vit C. Research has also shown that during infxns humans will increase the precursors to vit C (possibly trying to push the [non-existent] pathway?)

- **PMID: 1962571**; Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. *Am J Clin Nutr.* 1991 Dec;54(6 Suppl):1203S-1208S. Review.

Dosage: The usual dosage range is 200-3,000 mg/day. Larger doses (often up to bowel tolerance) have been used for some conditions. Bowel tolerance is determined by ingesting vitamin C in gradually increasing doses (usually 3-6 times per day) until abdominal pain and/or diarrhea occur, and then reducing the dose to a level at which these symptoms do not occur. High Vit C increases water in bowel→diarrhea. Vitamin C (pH neutralized) has been used intravenously, in doses of 25-50 g or more, to treat patients with viral infections.*

Certain anaerobic bacteria take Vit C and make gas. There is differential absorption of vit C depending on the individual. Studies show that 400-500g is maximal absorption of vit C in terms of increasing serum levels. Other studies show a vast improvement in 1g dose vs 200mg. Maybe we absorb more when our body needs it??

Vitamin C for oral administration is available as ascorbic acid, or in buffered forms (such as sodium ascorbate and calcium ascorbate). The latter are somewhat better tolerated by the gastrointestinal tract; however, with large doses, the increased intake of sodium or calcium must be taken into consideration. Approximately 12% of the total weight of sodium ascorbate and calcium ascorbate is sodium or calcium, respectively. Although "Ester C" has been claimed to be a more potent form of vitamin C than ascorbic acid, there is little or no research to support this claim.* Several manufacturers tout their vitamin C as being from

hypoallergenic sources, although no reports of allergy to oral vitamin C have been published. High dose could theoretically cause haptin rxns (Vit C + another molec join up forming an antigenic compound). Dr B doesn't think there's a big difference btwn the different sources of Vit C.

Interactions:

1) Aspirin and tobacco smoke may promote vitamin C deficiency. Large doses of vitamin C may interfere with some narcotics and some general anesthetics. There is conflicting research on whether vitamin C (1,000 mg/day or more) increases the bioavailability of oral contraceptives.

- **PMID: 12049152**; Effect of other drugs and chemicals on the degradation of aspirin in vitro: possible extrapolation to in vivo metabolism of aspirin. *Eur J Drug Metab Pharmacokinet.* 1979;4(2):103-8.
- **PMID: 15053335**; Antioxidant vitamins levels--nutrition and smoking. *Bratisl Lek Listy.* 2003;104(12):411-4.
- **PMID: 12264750**; Drug interactions with oral contraceptive steroids. *IPPF Med Bull.* 1983 Feb;17(1):1-2.

2) A dose of 16 g/day of vitamin C was associated with an increased requirement for warfarin in one patient; 1,000 mg/day of vitamin C did not interfere with the effect of warfarin in other patients. Animal studies on the relationship between vitamin C and warfarin have yielded conflicting results.

3) The absorption of iron is enhanced by vitamin C. Large doses of vitamin C may induce copper deficiency. Concomitant administration of vitamin C may inactivate sodium selenite, but not organic forms.

- **PMID: 14641967**; Iron absorption from ferrous fumarate in adult women is influenced by ascorbic acid but not by Na₂EDTA. *Br J Nutr.* 2003 Dec;90(6):1081-5.
- **PMID: 12049152**; Impact of tofu or tofu + orange juice on hematological indices of lacto-ovo vegetarian females. *Plant Foods Hum Nutr.* 2002 Spring;57(2):197-204.

Toxicity:

1) Abdominal pain and diarrhea: These side effects occur commonly with high doses. The "bowel tolerance" dose varies from person to person and may increase during acute illness. Gastrointestinal side effects may be eliminated by reducing the dose, taking vitamin C in divided doses, taking the vitamin with meals, or using buffered forms of vitamin C. Breast-fed infants may develop colic if their mother ingests large doses of vitamin C.

- Food and Nutrition Board, Institute of Medicine. *Vitamin C. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.* Washington D.C.: National Academy Press; 2000:95-185.

2) Hemolysis in G6PD deficiency: Intravenous administration of 80 g of vitamin C on 2 consecutive days was followed by hemolysis, acute renal failure and death in a patient with glucose-6-phosphate dehydrogenase deficiency.* G6PD deficiency makes the blood hemolyze under oxidative stress. Especially think about this w/ Mediterranean populations (Greece, turkey, southern italy). Recommend testing for this condition if you are going to use high dose Vit C.

3) Kidney Stones: Vitamin C does not appear to cause kidney stones in the general population,* as this has not appeared as a side effect in clinical trials. This has long been suspected to be associated with vitamin C use, since a case report was published in the early 1970's. Some studies have shown that use of as little as 1 gram of vitamin C per day can increase urinary oxalate levels. If giving high dose Vit C w/ Hx of oxalate kid stones consider measuring urinary oxalate levels and if they ↑ then consider a different therapeutic.

- **PMID: 12631089;** Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int.* 2003 Mar;63(3):1066-71.

4) "Rebound scurvy:" Abrupt discontinuation of large doses may rarely cause bleeding gums or other manifestations of mild vitamin C deficiency. However, the claim that rebound scurvy can develop in infants whose mothers took vitamin C during pregnancy is questionable.*

5) Iron overload: Ingestion of vitamin C may increase iron absorption, which could cause problems in individuals genetically predisposed to iron overload.

- **PMID: 15148082;** High-dose vitamin C and iron overload. *Ann Intern Med.* 2004 May 18;140(10):846; author reply 846-7.
- **PMID: 13679342;** Iron overload related to excessive vitamin C intake. *Ann Intern Med.* 2003 Sep 16;139(6):532-3.

6) Laboratory tests: Large doses of vitamin C may interfere with some stool tests for occult blood and some urine tests for glucose.* Good test question.

- **PMID: 6695884;** The Hemo-matic Analyzer: a new occult blood testing device. *Am J Gastroenterol.* 1984 Feb;79(2):117-21.

Flavonoids

Biochemistry: There are literally hundreds of flavonoids found in various fruits and vegetables. Many of these have been isolated and researched for therapeutic use. Flavonoids are generally potent antioxidants. Many of them help reduce capillary fragility. Others are antihistamine, anti-inflammatory, and anticancer. Flavonoids are similar in structure to steroid hormones, and some flavonoids have weak hormone-like actions. Some flavonoids are water soluble (proanthocyanodins) and some are fat soluble (quercetin) Flavonoids tend to be safe and have an affinity for the vasculature (Ix for venous and arterial conditions). Relationship btwn flavonoids and vit c→early research identified flavonoids (vit P) and vit C at same time. Found that Vit c and flavonoids work better together than either alone (synergistic relationship). Esperidin→ comes from citrus fruits and helps w/ hot flashes.

- **PMID: 14988447**; Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. *J Nutr.* 2004 Mar;134(3):562-7.
- **PMID: 14609128**; Inhibitory activity of flavonoids from *Prunus davidiana* and other flavonoids on total ROS and hydroxyl radical generation. *Arch Pharm Res.* 2003 Oct;26(10):809-15.

Indications:

- 1) **Capillary fragility:** Hesperidin (sometimes referred to in older research as vitamin P) has been reported to reduce capillary fragility. First reported in *JAMA* in 1940. Horse chestnut is also used for capillary fragility. Also proanthocyanodins (pycnogenol- patented form). Dr B would use a combination of hesperidin, horse chestnut and dietary sources of proanthocyanodins.
 - **PMID: 8376915**; A double-blind, placebo-controlled trial of a new veno-active flavonoid fraction (S 5682) in the treatment of symptomatic capillary fragility. *Int Angiol.* 1993 Mar;12(1):69-72.
 - 2) **Venous insufficiency:** Controlled trials exist for rutin, proanthocyanidins, horse chestnut and butcher's broom.
 - **PMID: 12771852**; Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. *Int Angiol.* 2003 Mar;22(1):24-31.
*Daflon = 90% diosmin, 10% hesperidin
 - **PMID: 12487623**; Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs.* 2003;63(1):71-100.
 - 3) **Hemorrhoids:** Most, but not all, double-blind trials have shown flavonoid extracts (particularly the semi-synthetic hydroxyethylrutosides) to be beneficial in the treatment of hemorrhoids.
 - **PMID: 10931020**; Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids. *Br J Surg.* 2000 Jul;87(7):868-72.
 - **PMID: 10813126**; Micronized purified flavonoid fraction compared favorably with rubber band ligation and fiber alone in the management of bleeding hemorrhoids: randomized controlled trial. *Dis Colon Rectum.* 2000 Jan;43(1):66-9.
 - 4) **Allergies:** Many physicians have used quercetin to treat hay fever symptoms, although no studies have been published to support its efficacy. Quercetin inhibits test tube degranulation of mast cells but can't reach these levels in serum. Other possible mechanisms: Quercetin inhibits inflammatory response and may affect mast cells in the gut (not needed to be systemically absorbed)
 - **PMID: 15330009**; Mast cells and mast cell mediators as targets of dietary supplements. *Ann Allergy Asthma Immunol.* 2004 Aug;93(2 Suppl 1):S24-34.
 - **PMID: 12883826**; Inhibitory effect of catechin against the superantigen staphylococcal enterotoxin B (SEB). *Arch Dermatol Res.* 2003 Sep;295(5):183-9. *Epub* 2003 Jul 17.
 - 5) **Prostatitis:** 500 mg bid of quercetin reduced symptoms in a double-blind placebo controlled trial. Interstitial cystitis→sterile inflammatory condition more likely in women. Some authors have hypothesized that IC in women is same condition as prostatitis in men. Quercetin has been shown effective in both conditions. These studies show that quercetin is absorbed (about 25% of the oral dose).
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- **PMID: 10604689**; Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. *Urology*. 1999 Dec;54(6):960-3.
- 6) **Hot flashes:** At least two double-blind studies have shown a reduction in hot flashes in women taking soy isoflavones. This treatment does not appear to be successful in women who have undergone treatment for breast cancer. Dr B has not seen this be effective.
- **PMID: 15243277**; Effects of genistein on hot flushes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study. *Menopause*. 2004 Jul-Aug;11(4):400-4.
 - **PMID: 12218721**; Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause*. 2002 Sep-Oct;9(5):329-34.
- 7) **Interstitial cystitis:** Quercetin has been reported to be beneficial in a small pilot trial.
- **PMID: 11272677**; *Tech Urol*. 2001 Mar;7(1):44-6.

Dosage: Will vary for different preparations.

Interactions: Certain flavonoids, particularly those in grapefruit, have been shown to alter activity of cytochrome p450 enzymes (phase I detox enzyme). Those, again like grapefruit, that alter the 3A4 isoenzyme (responsible for metabolism of about ½ of all pharmaceutical drugs) will have multiple important drug interactions. Grapefruit juice will inhibit this enzyme leading to increased drug levels. Research in this area is new, and unfortunately very incomplete. If you are seeing side effects in a pt that you don't expect look at diet and try to identify specific flavanoids showing up in diet. U of Indiana table will show meds and how it's cleared from diet (<http://medicine.iupui.edu/flockhart/>). Indol-3-carbinol and St John's wort will increase p450 enzyme levels, thus decreasing serum levels of drugs/compounds metabolized by this enzyme.

- **PMID: 1617681**; Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. *Cancer Res*. 1992 Jul 15;52(14):4050-2.
- **PMID: 10332534**; Probable antagonism of warfarin by green tea. *Ann Pharmacother*. 1999 Apr;33(4):426-8.
- **PMID: 11029010**; Effect of tea and other dietary factors on iron absorption. *Crit Rev Food Sci Nutr*. 2000 Sep;40(5):371-98. Review.
- **PMID: 11796378**; Epigallocatechin gallate synergistically enhances the activity of carbapenems against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2002 Feb;46(2):558-60.

Toxicity: Quercetin has been found to be mutagenic in vitro, and carcinogenic in one (but not in the majority) animal study. The clinical significance of this finding is not clear.

- **PMID: 12469199**; Quercetin regulates growth of Ishikawa cells through the suppression of EGF and cyclin D1. *Int J Oncol*. 2003 Jan;22(1):159-64.
 - **PMID: 11506819**; Dietary supplementation with the anti-tumour promoter quercetin: its effects on matrix metalloproteinase gene regulation. *Mutat Res*. 2001 Sep 1;480-481:269-76.
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Vitamin D

Biochemistry: Vitamin D is a hormone that is primarily responsible for regulation of calcium homeostasis. Vitamin D is also involved in differentiation of certain cell lines (stem cells to specific organ cells→kidney cell. CA cells de-differentiate). Vitamin D improves insulin sensitivity and increases insulin production in at least some patients.

Dr Vasquez article on new research on vit D.

Indications:

- 1) Prevention and treatment of osteoporosis, osteomalacia, rickets:** In addition to its well known bone-preserving effect, vitamin D supplementation (800 IU/day) reduced the risk of falls by 49% in one double-blind trial. This effect was presumably due to an improvement in balance and muscle strength resulting from vitamin D supplementation. Numerous studies have found vitamin D to be beneficial, together with calcium, for the treatment of osteoporosis. **People who take vit D for prevention of osteoporosis not only have less loss in bone density, they are also less likely to fall. People who are taking vit D have better proprioceptive sense. This may be on exam.**
 - **PMID: 12540414;** Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am J Clin Nutr.* 2003 Feb;77(2):504-11.
 - **PMID: 7733040;** Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D. *Am J Clin Nutr.* 1995 May;61(5):1140-5.
 - **PMID: 9278463;** Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.* 1997 Sep 4;337(10):670-6.
 - 2) Vitamin D-deficiency myopathy:** 5 cases of severe, but reversible, proximal myopathy due to vitamin D deficiency have been reported. Vitamin D deficiency may cause symptoms resembling chronic fatigue syndrome or fibromyalgia, according to one report. This is emerging data and Dr B thinks this area of research will erupt in next 10yrs.
 - **PMID: 6308041;** Vitamin D Deficiency, hypocalcemia, and increased skeletal muscle degradation in rats. *J Clin Invest.* 1983 Jul;72(1):102-12.
 - 3) Psoriasis:** 1,25-dihydroxyvitamin D₃ (orally or topically), calcipotriol (topically) and 1alpha-hydroxyvitamin D₃ (orally or topically) have each been found to be successful (uncontrolled and double-blind trials).
 - **PMID: 15244317;** Calcipotriol cream in the treatment of flexural psoriasis. *Int J Tissue React.* 2003;25(4):127-30.
 - **PMID: 15175024;** *J Invest Dermatol.* 2004 Jun;122(6):1356-64.
 - 4) Polycystic ovaries:** 50,000 IU of vitamin D (ergocalciferol), 1-2 times per week, plus 1,500 mg/day of calcium, resulted in normalization of menstrual periods in 7 of 13 women after 2 months (uncontrolled trial). PCOD→hirsutism, amenorrhea, ↑weight (due to insulin resistance). Recommendations: ↓ complex carbs, ↑ fiber
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(pulls hormones out of body by binding them in GI→testosterone is main hormone out of balance here), exercise.

- **PMID: 10433180**; Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. Steroids. 1999 Jun;64(6):430-5.

5) Seasonal mood disorders: Supplementation with 400 or 800 IU/day for 5 days during the winter enhanced mood in healthy student volunteers (double-blind study).

- **PMID: 9539254**; Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology (Berl). 1998 Feb;135(4):319-23.

6) Scleroderma: 1,25-dihydroxyvitamin D₃, given orally for 6 months to 3 years, has been reported to improve the skin manifestations of scleroderma (uncontrolled trials).

- **PMID: 14660267**; Topical calcipotriol ointment in the treatment of morphea. J Dermatolog Treat. 2003 Dec;14(4):219-21.
- **PMID: 10599359**; Treatment of generalized morphea with oral 1,25-dihydroxyvitamin D₃. Adv Exp Med Biol. 1999;455:299-304.

7) Prostate cancer: 2,000 IU/day of vitamin D (ergocalciferol) plus 500 mg/day of calcium for 12 weeks improved bone pain in 4 of 16 patients and increased muscle strength in 6 of 16 patients (uncontrolled trial). * Vitamin D (active form) plus the chemotherapy agent taxotere was associated with a high response rate in advanced prostate cancer. Two other small studies have shown that high dose active vitamin D can help a small percentage of patients with advanced disease achieve stabilization. One of Dr B's favorite Tx for prostate CA. Shown to ↓ symptoms and ↓ PSA levels. Has been shown to slow progression of prostate CA.

- **PMID: 14519629**; Clin Cancer Res. 2003 Sep 15;9(11):4077-83
- **PMID: 10604343**; J Urol. 2000 Jan;163(1):187-90
- **PMID: 12506180**; J Clin Oncol. 2003 Jan 1;21(1):123-8

8) Malabsorption of fat soluble vitamins: People suffering from Crohn's disease and cystic fibrosis will often require vitamin D supplementation to maintain serum levels. **For mid-term: be able to ID some fat soluble vitamins and fat soluble vit malabsorptive dz's**

- **PMID: 14717616**; Management of osteoporosis in adults with cystic fibrosis. Drugs. 2004;64(2):133-47. Review.

9) Migraines: The combination of 50,000 IU of vitamin D per week, together with 1 - 2 grams of calcium per day, was associated with reduction of symptoms in women with menstrual migraines. Side note: Ocular migraines can result in visual changes w/o any pain. Menstrual migraines are associated w/ greater than normal drops in estrogen before menstruation. Dr B thinks it's likely the Ca binding to the hormones in the gut and causing precipitation and excretion.

- **PMID: 7843955**; Alleviation of migraines with therapeutic vitamin D and calcium. Headache. 1994 Nov-Dec;34(10):590-2.
 - **PMID: 8002332**; Vitamin D and calcium in menstrual migraine. Headache. 1994 Oct;34(9):544-6.
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Dosage: For most uses, between 200 – 1000 IU are sufficient. Estimated maximum endogenous production upon sunlight exposure is 10,000 IU per day. National Academy of Sciences safe upper limit is 2000 IU per day. Activated forms like calcitriol are used in much smaller doses, often less than 1 mcg per day. Patients with renal disease may require supplementation with active form.

1,25 (D3/calcitriol) is active form. Vit d is activated in liver and kid. Consider supplementing in kid and liv failure pts. OD of vit D→hypercalcemia→HTN, arrhythmia, confusion (may look like a stroke). When you use the active form of vit D you bypass the regulatory steps and have a higher risk of OD.

Toxicity: Published cases of vitamin D toxicity all involve intakes of at least 40,000 IU/day. Calcitriol (1,25-dihydroxyvitamin D₃) should be used with caution and monitored appropriately. Toxicity is usually due to hypercalcemia.

- **PMID: 10232622;** Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999 May;69(5):842-56.
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Vitamin E

Biochemistry: Vitamin E is a group of eight different tocopherols or tocotrienols that act as lipid soluble antioxidants. Most supplements contain the predominant form alpha-tocopherol. Although some basic science research exists on the different forms of vitamin E, the differences between the various sub-forms of vitamin E have not been studied in humans. Vitamin E deficiency causes infertility in animal studies. There is not known to be sn/sx's associated w/ vit E deficiency in humans.

Most supplements that call themselves vit E are actually alpha tocopheral (may be synthetic or natural source). Unlike beta-carotene, no research has looked at whether or not there is a difference bwtm the different forms.

Indications:

1) Cardiovascular disease (prevention and treatment):

- Myocardial infarction:** Supplementation with 100-400 IU/day may reduce the risk of myocardial infarction (double-blind trials, conflicting results, with more negative than positive results). 1st study showed a dramatic reduction in non-fatal heart attacks (didn't protect against fatal heart attacks). Second study showed no benefit. Vit E has some nice cardiovascular actions, but it may not prevent heart attacks. Interventions like the Mediterranean or ornish diet along w/ exercise are proven to be preventative.
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- **PMID: 8209876**; Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol.* 1994 Jun 15;139(12):1180-9.
- **PMID: 8479464**; Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med.* 1993 May 20;328(20):1450-6.
- **PMID: 11738275**; Antioxidant vitamins and the risk of carotid atherosclerosis. The Perth Carotid Ultrasound Disease Assessment study (CUDAS). *J Am Coll Cardiol.* 2001 Dec;38(7):1788-94.
- **PMID: 14633812**; Diabetes Care. 2003 Dec;26(12):3264-72

b. Intermittent claudication: Supplementation with 400-1,600 IU/day for at least 3 months increased walking distance (double-blind trials). IC=leg pain w/ exercise due to narrowing of arteries→arterial insufficiency of lower extremities. Stents and Pentoxifylline are conventional Tx. Vit E does work well for this. Mechanism: hypothesized having to do w/ ↓LDL oxidation or ↓platelet activation

- **PMID: 11266271**; Antioxidants reduce oxidative stress in claudicants. *J Surg Res.* 2001 Apr;96(2):183-7.
- **PMID: 10791562**; Prospective study of diet, lifestyle, and intermittent claudication in male smokers. *Am J Epidemiol.* 2000 May 1;151(9):892-901.
- **PMID: 10796571**; Cochrane Database Syst Rev. 2000(2):CD000987

2) Gynecological conditions:

a. Fibrocystic breast disease (600-800 IU/day): Results have been conflicting – uncontrolled trials showed benefit, whereas a 2-month double-blind trial showed no effect. Maximal affect after 2-3 cycle of being on E.

- **PMID: 7411752**; Vitamin E relieves most cystic breast disease; may alter lipids, hormones. *JAMA.* 1980 Sep 5;244(10):1077-8.
- **PMID: 11103660**; Potential mechanisms of diet therapy for fibrocystic breast conditions show inadequate evidence of effectiveness. *J Am Diet Assoc.* 2000 Nov;100(11):1368-80.

b. Premenstrual syndrome: Supplementation with 600 IU/day relieved symptoms of PMS in a double-blind study.

- **PMID: 3302248**; Efficacy of alpha-tocopherol in the treatment of the premenstrual syndrome. *J Reprod Med.* 1987 Jun;32(6):400-4.

c. Menopausal hot flashes: Supplementation with 400-800 IU/day appears to be occasionally helpful. Improvement has been reported in several uncontrolled trials, whereas no benefit was found in controlled studies. Unesterified tocopherols appear to be more effective than esterified forms of vitamin E (clinical observation). Dr B's favorite Tx for hot flashes (esp those w/ Hx of breast CA- may not want to use isoflavones w/ these pts)

- **PMID: 12440557**; Pathophysiology and treatment of hot flashes. *Mayo Clin Proc.* 2002 Nov;77(11):1207-18. Review. Erratum in: *Mayo Clin Proc.* 2004 Aug;79(8):1088.

d. Dysmenorrhea: Supplementation with 150 IU/day for 2-3 menstrual cycles significantly reduced symptoms compared with placebo (double-blind trial).

- **PMID: 11762659**; A randomised placebo-controlled trial to determine the effect of vitamin E in treatment of primary dysmenorrhoea. *BJOG.* 2001 Nov;108(11):1181-3.

- 3) **Epilepsy:** In a double-blind trial, administration of 400 IU/day reduced seizure frequency by at least 60% in 10 of 12 children with epilepsy, whereas none of 12 children in the placebo group showed that degree of improvement. May consider adding if conventional Tx not controlling it (also consider taurine).
- **PMID: 11846625;** Catalase and alpha-tocopherol attenuate blood-brain barrier breakdown in pentylentetrazole-induced epileptic seizures in acute hyperglycaemic rats. *Pharmacol Res.* 2002 Feb;45(2):129-33.
 - **PMID: 11163018;** Oxidative stress and antioxidants in epilepsy. *Clin Chim Acta.* 2001 Jan;303(1-2):19-24.
- 4) **Chronic hepatitis:** Of 12 patients with hepatitis B treated with 600 IU/day of vitamin E for 9 months, 5 had a complete response, compared with none of 12 in an untreated control group. In 6 patients with hepatitis C refractory to interferon therapy, vitamin E (1,200 IU/day for 8 weeks) appeared to prevent hepatic fibrosis. Because Liv CA tends to arise in fibrotic tissue this Tx could theoretically also prevent liv CA. Another thing Dr B likes for hepatitis →Kampo formulations available at <http://www.honso.com/> (SHO-SAIKO-TO=bluplurium formula→bluplurium, licorice, ginseng, ginger, scutellaria, jejube, pinellia tuber)-traditional Chinese formula studied by Chinese gov't. Good formula for Hep C→prevents hepatocellular CA. Data out of japan showing ↓ liv CA in Hep B rats w/ this formula.
- **PMID: 11248360;** Vitamin E as treatment for chronic hepatitis B: results of a randomized controlled pilot trial. *Antiviral Res.* 2001 Feb;49(2):75-81.
- 5) **Cancer prevention:** 55 IU of vitamin E per day resulted in a reduction of 32% in prostate cancer incidence. A non-significant 22% reduction in colon cancer incidence was seen in the same study.
- **PMID: 15084515;** Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. *FASEB J.* 2004 Jun;18(9):1019-21. Epub 2004 Apr 14.
 - **PMID: 15048090;** RRR-alpha-tocopheryl succinate inhibits human prostate cancer cell invasiveness. *Oncogene.* 2004 Apr 15;23(17):3080-8.
- 6) **Rheumatoid arthritis:** Double-blind trials have found clinical benefit in rheumatoid arthritis at doses ranging from 600 – 1800 IU. Vit E inhibits production of TNF-a (pro-inflammatory cytokine).
- **PMID: 11840456;** Vitamin E uncouples joint destruction and clinical inflammation in a transgenic mouse model of rheumatoid arthritis. *Arthritis Rheum.* 2002 Feb;46(2):522-32.
 - **PMID: 11367869;** Antioxidants as adjuvant therapy in rheumatoid disease. A preliminary study. *Arzneimittelforschung.* 2001;51(4):293-8.
 - **PMID: 11121721;** Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. *Free Radic Biol Med.* 2000 Dec;29(11):1135-42.
- 7) **Cold sores:** Topical application of vitamin E has been reported to speed healing of cold sores. Dr B also uses Vit E for chemo induced mouth sores→bite into a Vit E cap. Dr B recommends lemon balm extract for prodrome phase.
- **PMID: 9477116;** Evaluation of antioxidant healing formulations in topical therapy of experimental cutaneous and genital herpes simplex virus infections. *Antiviral Res.* 1997 Dec;36(3):157-66.
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8) **Hypertension:** 200 IU of vitamin E for 6 months significantly reduced systolic and diastolic blood pressure in a double-blind clinical trial. Small but statistically significant affect on HTN.

- **PMID: 14749737;** Long-chain polyunsaturated fatty acids interact with nitric oxide, superoxide anion, and transforming growth factor-beta to prevent human essential hypertension. *Eur J Clin Nutr.* 2004 Feb;58(2):195-203.
- **PMID: 12463106;** *Int J Vitam Nutr Res.* 2002 Oct;72(5):309-14

Dosage: Although clinical benefits have been seen with as low as 10-50 IU, most physicians recommend doses of several hundred IU. Safe upper limit has been defined as 1000 IU.

Vitamin E is listed in International Units (IU) and milligrams. For the naturally occurring form (d-alpha-tocopherol, also called RRR-alpha-tocopherol), 1 mg is approximately equivalent to 1.5 IU. For the synthetic form (d,l-alpha-tocopherol, also called all-rac-alpha-tocopherol), 1 mg is equivalent to 1 IU.* Know difference of dosages for different vit E forms for NPLEX (dr. B won't test us on it)

Interactions:

- 1) **Phenothiazines:** Vitamin E (800-1,600 IU/day) reduced the severity of tardive dyskinesia (tics→robert deniro in awakenings) caused by phenothiazines (double-blind trials). Patients with tardive dyskinesia for more than 5 years did not respond. Dr B would recommend this as more of a prevention than for an ongoing issue.
 - **PMID: 1707329;** Partial attenuation of chronic fluphenazine-induced changes in regional monoamine metabolism by D-alpha-tocopherol in rat brain. *Brain Res Bull.* 1991 Feb;26(2):251-8.
 - **PMID: 10624549;** The preventative role of antioxidants (selegiline and vitamin E) in a rat model of tardive dyskinesia. *Biol Psychiatry.* 1999 Dec 15;46(12):1672-81.
 - 2) **Warfarin:** An early case report suggesting that vitamin E increases the activity of warfarin has been refuted by a controlled trial. Vit E is not Cx in pts on warfarin. If someone is on a blood thinner and you want to add something that may affect bleeding time you need to monitor bleeding times.
 - **PMID: 8629604;** Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol.* 1996 Mar 1;77(7):545-6. (negative correlation)
 - 3) **Chemotherapy side effects:** Vitamin E (300 IU/day) reduced the incidence of cisplatin-induced neurotoxicity. Vitamin E was begun 1-8 days prior to the start of chemotherapy and was continued for 3 months after the end of chemotherapy. In a study in mice, vitamin E did not inhibit the antitumor effect of cisplatin.
 - **PMID: 15159233;** Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. *Am J Clin Nutr.* 2004 Jun;79(6):1029-36.
 - **PMID: 12610195;** Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol.* 2003 Mar 1;21(5):927-31.
 - 4) **Iron:** Vitamin E and iron exert mutually inhibitory effects.
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- **PMID: 11440839**; The antioxidant properties of zinc: interactions with iron and antioxidants. *Free Radic Biol Med.* 2001 Jul 15;31(2):266-74.

5) **Polyunsaturated fatty acids:** Administration of polyunsaturated fatty acids (either omega-6 or omega-3) may increase the requirement for vitamin E. Ignore this interaction→new study refuted this.

- **PMID: 10804454**; Relationship between vitamin E requirement and polyunsaturated fatty acid intake in man: a review. *Int J Vitam Nutr Res.* 2000 Mar;70(2):31-42. Review.

6) **Other antioxidants:** Vitamin E enhances the therapeutic effect of vitamin A, as well as some of the actions of selenium.

- **PMID: 12008975**; Immunoregulatory and antioxidant performance of alpha-tocopherol and selenium on human lymphocytes. *Biol Trace Elem Res.* 2002 May;86(2):123-36.
- **PMID: 8579372**; Synergistic interactions between vitamin A and vitamin E against lipid peroxidation in phosphatidylcholine liposomes. *Arch Biochem Biophys.* 1996 Feb 1;326(1):57-63.

Toxicity: The highest level human studies have used 3200 IU of vitamin E per day. No significant toxicity has been demonstrated, even at the higher doses. Doses in animal studies roughly equivalent to a 50,000 IU human doses have been reported to increase bleeding time. These studies have been occasionally been used as a caution against high dose vitamin E (see interaction 2 above).

One study showed an increase in rates of infection in elderly people taking 200 IU per day of vitamin E. Another study showed 600 IU of vitamin E led to a measurable impairment in glucose tolerance (in contrast to other studies in diabetics).

People taking 400IU/day Vit E found more hemorrhagic strokes and less occlusive strokes.

Studies looked at Vit E on scar tissue formation→most showed no benefit and one showed that it made the scarring worse→may be due to increased infxn. Dr B likes using systemic anti-inflammatories instead of local Tx's

Vitamin K

Biochemistry: Vitamin K is necessary to utilize several of the blood clotting factors. It is also necessary for bone production. K stands for coagulation (in german). K dependant clotting factors are 2,7,9,11. Warfarrin is an antagonist for vit K. May need to use vit K in warfarrin pts if they have over dosed on warfarrin. INR=figured value based on bleeding times→generally kept btwn 2-3 to prevent adverse risk. If INR is >5-6→refer to hospital. Dietary factors, exercise, hydration can affect INR levels. ↓INR→more clotting. ↑INR→↑thinning→↓clotting

- **PMID: 9279066**; Skeletal functions of vitamin K-dependent proteins: not just for clotting anymore. *Nutr Rev.* 1997 Jul;55(7):282-4.

Indications:

- 1) **Blood clotting:** Treatment of blood clotting disorders resulting from vitamin K deficiency. Vitamin K can also be used to reverse overdose with coumadin.
 - **PMID: 3184567;** Vitamin K reversible hypoprothrombinemia in rats. II. Efficacy of vitamin K on latamoxef-induced coagulopathy in rats. *Jpn J Pharmacol.* 1988 Aug;47(4):357-65.
 - **PMID: 14670783;** Brain haemorrhage in five infants with coagulopathy. *Arch Dis Child.* 2003 Dec;88(12):1119-21.

- 2) **Prevention and treatment of osteoporosis:** Supplementation with 1,000 mcg/day of vitamin K₁ reduced urinary calcium loss in postmenopausal women (uncontrolled trials). Supplementation with menatetrenone (vitamin K₂; 45 mg/day) reduced bone loss and fracture incidence in postmenopausal women (controlled trials). Vitamin K₂ is now available in the United States. Vit K is needed for osteocalcin→protein involved in ossification of bone. High dose vit K shown to increase bone density and decrease Fx. Flouride will increase bone density but may make bone more likely to Fx.
 - **PMID: 11793169;** Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. *J Orthop Sci.* 2001;6(6):487-92.
 - **PMID: 14506950;** Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif Tissue Int.* 2003 Jul;73(1):21-6.

- 3) **Nausea and vomiting of pregnancy:** 5 mg/day of vitamin K₃ (menadione) plus 25 mg/day of vitamin C relieved symptoms within 3 days in 91% of 70 women (uncontrolled trial). Treatment was continued for an average of 30 days. Vitamin K₃ alone was less effective. Vitamin K₃ is no longer used, because of potential toxicity; it is not known whether vitamin K₁ is effective. Dr B doesn't think K₁ works for this.
 - **PMID: 13593050;** [Results obtained with a mixed drug containing menadione & vitamin C in 88 cases of nausea & vomiting in pregnancy.] *Union Med Can.* 1958 Oct;87(10):1204-5.

- 4) **Chronic pain due to cancer:** Daily intramuscular injections of 20-30 mg of vitamin K (type not specified) effectively relieved pain in 83% of 115 cancer patients (uncontrolled trial). The frequency of administration may be reduced as improvement occurs (clinical observation – Lamson D).*

- 5) **Myelodysplastic syndrome (and perhaps other cancers):** A preliminary study from Japan found 45 mg of vitamin K₂ to be an active treatment in patients with myelodysplastic syndrome. Test tube studies have shown anti-cancer effects of vitamin K₂ in many different cell lines (see review article by Lamson / Plaza in *Alt Med Rev*). Myelodysplastic synd=Terminal condition in which pts require multiple transfusions and can get Fe overload and/or blast crisis. Dr B likes K₂ and D as a therapeutic for blood CA→K₂ and D are prodifferentiating factors which are helpful in leukemias.
 - **PMID: 11807630;** *Ann Hematol.* 2002 Jan;81(1):16-9. Epub 2001.

Dosage: The RDA for vitamin K is 65 mcg/day for adult females and 80 mcg/day for adult males. Usual supplementary doses are 100-1,000 mcg/day. Larger doses (5-45 mg/day) have been used for specific conditions. Vitamin K₁ (phylloquinone) is

synthesized by plants, and vitamin K₂ (a family of chemically related molecules) is synthesized by animals and bacteria. Although all of the forms of vitamin K are known to have "vitamin K activity," it is not known whether they are all effective for each of the various conditions listed.* Previously available i.m. preparations of vitamin K were K₃, and likely quite different biochemically than currently available sources. Injectable vitamin K₃ does not appear to be commercially available at the present time. K₁, K₂, K₃ will all help w/ clotting disorders due to a deficiency. Vit K is similar in structure to CoQ10→may be a cheaper way to improve electron transfer in conditions like Parkinson.

Pts at risk for K def→malabsorption, institutionalized elderly (on Abx→↓gut flora, on warfarin), Painless shortness of breath→pulmonary embolism. Unilateral Swelling of extremity→DVT (esp common in pancreatic CA)

Interactions: All forms of vitamin K are strictly contraindicated with warfarin. Vitamin K containing foods also should be monitored during anti-coagulant therapies.

- **PMID: 10568341**; Vitamin K: a practical guide to the dietary management of patients on warfarin. Nutr Rev. 1999 Sep;57(9 Pt 1):288-96.
- **PMID: 14565795**; Multivitamin supplements may affect warfarin anticoagulation in susceptible patients. Ann Pharmacother. 2003 Nov;37(11):1603-6.

Toxicity: Generally well tolerated at the usual doses. There are no reports of vitamin K₁ toxicity at doses up to 500 times the RDA. However, additional research is needed to determine the safety of long-term use of high doses. Adverse effects have been reported with the use of the vitamin K precursor menadione, and its water-soluble derivative menadiol (Synkavite); these products are no longer used.* It is important to note that although deficiency of vitamin K impairs the ability to form blood clots, megadoses do not increase the likelihood of clot formation.

Questions for discussion:

- 1) The evidence is conflicting about the ability of vitamin E to prevent serious cardiovascular events. What advice do you give to a patient interested in this therapy?
 - 2) Your patient is thinking of using intravenous vitamin C therapy to treat advanced cancer. Is this well supported with clinical research? Basic science research? What metabolic defect would you need to rule out first?
 - 3) Your patient on high-dose vitamin D supplementation presents with confusion and dizziness. What laboratory workup is indicated?
 - 4) Since vitamin K₂ works by increasing the activity of osteocalcin, would you or would you not use it concomitantly with calcium and vitamin D?
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