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## Vitamin C—Can a Tablet a Day Keep Colds Away?

*By Barak Gaster, MD*

WINTER MEANS ONE THING FOR MOST PRIMARY CARE PHYSICIANS. Colds, colds, colds. And if you're like me, it also means an almost ritualistic, somewhat paranoid, chap-inducing commitment to hand washing. It's a desperate attempt to achieve the impossible—to spend each and every day surrounded by upper respiratory infections while not catching one myself.

As every "winter care" patient handout says, hand washing is the only sure-fire way to prevent colds. Or is it? If you remember Linus Pauling, not only as a Nobel-winning chemist but also as a crusader, you're also probably aware of one of the oldest controversies in evidence-based medicine: Can vitamin C prevent the common cold? Twenty-six years after the publication of Pauling's book *Vitamin C and the Common Cold*, the answer is quite clear. High doses of vitamin C do not prevent colds, although they may slightly lessen their severity and duration.

### Pharmacology and Mechanism of Action

Vitamin C (ascorbic acid) is an essential, water-soluble vitamin. It is found in high quantities in citrus fruits, strawberries, kiwi fruit, and tomatoes, and in lower quantities in potatoes and green leafy vegetables.

It is required for collagen formation and tissue repair and also plays a role in the metabolism of carbohydrates and the synthesis of proteins. It is this latter function that has been most widely linked to fighting infection, although specific effects of vitamin C on the immune system are unknown. Vitamin C has been shown to have both antioxidant and pro-oxidant effects.[1]

Vitamin C is well absorbed after oral dosing, although its bioavailability drops off considerably at doses greater than 1.5 g. At high serum concentrations, it is excreted unchanged in the urine. Serum levels tend to plateau at doses greater than 3 g per day.[2] Although vitamin C's clearance is proportional to its concentration at lower serum levels, once high serum levels are achieved, its $t_{1/2}$ is long and relatively constant (about 14 days). High intake may stimulate the

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## INSIDE

metabolism of vitamin C so that relative deficiency may occur if long-term administration of megadoses is abruptly discontinued.[3]

**Which of the following laboratory tests may be falsely negative in patients taking vitamin C?**

a. Urine pregnancy test
b. Stool occult blood test
c. Urine dipstick for glucose
d. b and c

## Clinical Studies

Over the past 25 years, there have been more than 60 randomized, controlled trials of vitamin C to prevent and treat the common cold. A recent meta-analysis, published as part of the Cochrane Library Project, pooled the data from 21 of the best of these trials, including more than 4000 subjects who had experienced a total of 5438 upper respiratory infections.[4]

The main conclusion of this meta-analysis was that vitamin C had no benefit on the incidence of the common cold, but that it did have a small, consistent benefit in decreasing the duration and severity of symptoms. This benefit was very modest, however, averaging no more than 0.5 symptom days per cold episode, or about 8% of symptom days.

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This small benefit was seen equally in studies that used prophylactic treatment throughout the winter months and in those that simply initiated high doses at the first signs of a cold (abortive therapy). There was also no clear evidence that one dosing regimen was better than another, although there was some suggestion from the abortive therapy trials that doses of 1 g or higher may be more effective than lower doses.

In the trial that received the highest methodological quality score in the Cochrane review, Anderson et al randomized 818 adults to take either 1 g of vitamin C daily for three months plus 4 g for the first three days of any illness or to take an identical number of placebo tablets.[5] The average number of cold episodes was 1.4 for those taking vitamin C vs. 1.5 for those taking placebo, a difference that was not significant. Those taking vitamin C had 21% fewer days of missed work ($P < 0.05$).

This same group of researchers from Toronto, Canada went on to publish two large follow-up studies to this one.[6,7] All three studies came to similar conclusions.

## Dosage

Most trials of prophylactic therapy have used 1 g once daily of vitamin C and most trials of abortive therapy have used 2 g or more per day divided into two-four equal doses. The ideal frequency of dosing has not been well-studied, although daily dosing has been shown to raise basal serum levels over time. In abortive therapy, where the objective is to raise serum levels very quickly, bid or tid dosing is probably appropriate. Cigarette smokers should use somewhat higher doses since smoking increases the metabolic turnover of vitamin C.[8]

The Reference Daily Intake (RDI), formerly the Recommended Daily Allowance (RDA), of vitamin C is 60 mg per day. An eight-ounce glass of orange juice contains about 100 mg of vitamin C.

## Formulation

Vitamin C tablets come most commonly in 500 mg sizes. There is no difference in biologic activity or bioavailability between vitamin supplements that claim to be "natural" and those that are synthesized chemically. Likewise, because vitamin C is so readily absorbed in any form, there is no indication that powders or citrus fruits have an advantage over tablets.

## Adverse Effects

Although mild side effects have been reported from doses of vitamin C greater than 1 g,[3] the medication appears to have been very well tolerated in the randomized trials. A few subjects report experiencing nausea, heartburn, gas, or diarrhea, especially with doses over 2 g, but they represent a very small percentage of the total

number of study subjects.

About 5% of individuals who take more than 1000 mg per day of vitamin C on a regular basis will develop hyperoxaluria, which could lead to kidney stones. Caution should be used in patients with a history of kidney stones or renal dysfunction.

### Interactions

Vitamin C has been shown to facilitate the absorption of iron and to decrease the excretion of aspirin. There are conflicting reports of vitamin C's effect on prothrombin times in patients taking warfarin. Vitamin C can cause false negative results in both stool occult blood testing and in routine urine dipstick tests for glucose.

### Conclusion

There is no evidence that vitamin C can prevent the common cold. Almost all studies, however, have demonstrated a small decrease in the duration of cold symptoms with either daily dosing through the winter months or with abortive therapy at the first signs of a cold.

### Recommendation

Given the benefit of slightly decreasing the time missed from work and the apparent safety and low cost of vitamin C, I would recommend abortive therapy for motivated patients, especially for those whom you suspect have a low dietary intake of vitamin C, such as college students and the elderly.[9,10] ❖

*Dr. Gaster is an Acting Assistant Professor of Medicine at the University of Washington in Seattle.*

## Linus Pauling: Maverick or Messiah?

Few scientists in the 20th century have engendered as much controversy as Linus Pauling. Having first won a Nobel Prize in chemistry in 1954 for his use of quantum mechanics to elucidate the nature of chemical bonds, he again gained international attention in 1962 by winning a Nobel Prize for peace for his work against nuclear weapons testing. It was his crusade on behalf of vitamin C beginning in the early 1970s, however, that won him lasting media fame.

In one of the first ever published meta-analyses, Pauling synthesized the results of four studies of exceedingly poor quality on the use of vitamin C for common colds and came to the astonishing conclusion that it could reduce their incidence by more than 50%. There ensued 21 years of best-selling books, lectures, and vitriolic debate, during which his growing zeal for what he called "orthomolecular" medicine led him to claim that high doses of vitamin C could treat everything from cancer to schizophrenia. As his zeal grew, however, so did his isolation from the mainstream scientific community.

By the time Pauling died in 1994, at the age of 93, he had increased his intake of vitamin C to 18 g/d (300 times the RDI), boosting his intake to 40 g/d at the first signs of a cold. After his death, his supporters wasted no time in attributing his longevity to, in part, the greater than 100 kg of vitamin C that he consumed in the last two decades of his life. ■

**Which of the following statements is true regarding vitamin C?**

a. It is a non-essential, fat-soluble vitamin.
b. It has been shown to decrease the incidence of the common cold.
c. It has been shown to decrease the duration of cold symptoms.
d. It is more effective when given as daily prophylactic therapy rather than as abortive therapy.

### References

1. Anonymous. Vitamin supplements. *Med Lett Drug Ther* 1998;40:75-77.
2. Angel J, et al. Effect of oral administration of large quantities of ascorbic acid on blood levels and urinary excretion of ascorbic acid in healthy men. *Int J Vitam Nutr Res* 1975;45:237-243.
3. Ascorbic Acid. In: *Drug Information*. 40th ed. Bethesda, Md: American Hospital Formulary Service; 1998:3013.
4. Douglas RM, et al. Vitamin C for the common cold. Available in The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration; Issue 3. Oxford: Update Software; 1998.
5. Anderson TW, et al. Vitamin C and the common cold: A double-blind trial. *Can Med Assoc J* 1972;107:503-508.
6. Anderson TW, et al. The effect on winter illness of large doses of vitamin C. *Can Med Assoc J* 1974;111:31-36.
7. Anderson TW, et al. Winter illness and vitamin C: The effect of relatively low doses. *Can Med Assoc J* 1975;112:823-826.
8. Kallner AB, et al. On the requirements of ascorbic acid in man: Steady-state turnover and body pool in smokers. *Am J Clin Nutr* 1981;34:1347-1355.
9. Johnston CS, et al. Vitamin C status of a campus population: College students get a C minus. *J Am Coll Health* 1998;46:209-213.

10. Pfitzenmeyer P, et al. Vitamin B6 and vitamin C status in elderly patients with infections during hospitalization. *Ann Nutr Metab* 1997;41:344-352.

# Selenium Supplementation for Cancer Prevention

*By Michael D. Cirigliano, MD and Philippe O. Szapary, MD*

RESPONSIBLE RESEARCH HAS ESTIMATED THAT DIETARY factors alone may be responsible for 30-60% of cancers.[1] Specific vitamins and minerals may help to prevent cancer.[2] Selenium, an essential trace element, has been the focus of animal and human studies in which it shows promise as an immunostimulant and antioxidant, and especially as a chemoprotective agent.

### Chemistry

The mineral selenium was first identified by John Jacob Berzelius in 1817 and belongs to the same group of elements as sulfur.[3] The element is found in nature both in organic and inorganic forms.[3] In common foods, selenium occurs as analogues of a variety of sulfur compounds, particularly sulfur amino acids.[4] The methylated and selenoamino acid forms of selenium appear to be of most importance in health and nutrition.[3] Inorganic forms of selenium, including sodium selenite and sodium selenate, as well as organic forms, including selenomethionine and as a selenium-enriched yeast, have all been used in cancer prevention studies.[3]

The cancer protective properties of selenium depend not only on its bioavailability but also on where the selenium moiety enters the metabolic pathway.[5] This has led to the conclusion that the chemical form of selenium ingested is important in determining its biological activity.[6]

### Normal Function and Mechanism of Action

Selenium plays an integral role in the normal function of selenoproteins in the body, required for normal health and cancer protection.[7] Deficiencies can lead to a number of disease states including liver cell necrosis, abnormal testosterone metabolism, cardiomyopathy (Keshan disease), and a deforming arthritis (Kashin-Beck disease).[3] Selenium plays a role in the normal function of other selenoproteins including iodothyronine deiodinase, which catalyzes thyroxine (T4) to tri-iodothyronine (T3) conversion.[8]

Several postulated mechanisms exist. Selenium is a component of the antioxidant enzyme glutathione peroxidase which protects against oxidative damage.[3] Free radicals are known to cause accelerated atherosclerosis, damage to DNA, and ultimately may lead to an increased risk of cancer.[9] A second mechanism involves carcinogen-induced tumors and evidence that selenium alters carcinogen metabolism resulting in the production of inactive compounds.[10] Third, selenium may improve T lymphocyte responsiveness and thereby enhance primary immunity.[11,12] Finally, production of cytotoxic selenium metabolites, inhibition of protein synthesis, inhibition of specific enzymes, and stimulation of apoptosis have all been postulated.[13]

### Animal Trials

Numerous animal studies support the hypothesis that elevated selenium levels decrease tumor incidence.[10,14] In mice and rats exposed to a variety of carcinogenic factors, supplemental selenium administration has led to a statistically significant reduction in cancers.[15] Reduction in tumor incidence ranging from 7% to 100% has been documented using skin, liver, hepatic, and colon cancer models.[16,17]

### Clinical Trials

For almost 30 years, epidemiological studies have revealed an inverse relationship between serum selenium levels and overall cancer mortality rates.[18,19] In regions with intermediate or high crop selenium levels, significantly lower cancer mortality rates have been noted for total cancer and cancers of the lung, colon and rectum, bladder, esophagus, pancreas, breast, ovary, and cervix.[20]

Several case-control studies have found lower serum selenium levels in cancer patients vs. controls.[21,22] In one study, selenium levels of 111 patients who went on to develop cancer over the next five years were compared to the selenium levels of 210 cancer-free patients matched for age, race, sex, and smoking history.[23] The mean selenium level of cancer patients was significantly lower than that of controls, with the strongest association found in patients with gastrointestinal and prostatic cancers. Other data are mixed;[24] tumor sequestration of selenium or poor dietary intake have been postulated.[3]

In 1996, Clark et al studied the effect of selenium supplementation for prevention of carcinoma of the skin.[13] This randomized, double-blind, placebo-controlled trial involved 1312 patients who either received placebo or 200 mcg of organic selenium (0.5 g of high selenium-enriched brewer's yeast) daily. No effect on reducing the incidence of new basal cell or squamous

cell skin cancers was noted.

Although there was no demonstrated benefit in their primary endpoint, review of secondary endpoints did show an overall significant decrease in incidence of specific cancers including lung, prostate, colon, and rectum, but not breast, within three to five years. Overall cancer incidence and mortality were both significantly reduced by 39% and 48% respectively.

The trial was unblinded in advance of its planned termination. Of those patients complaining of adverse effects, 21 were in the selenium group and 14 were in the placebo group. Most complained of gastrointestinal upset; plasma selenium concentrations from both groups were not significantly different and were well below toxic levels. The authors concluded that selenium treatment showed cancer-protective effects within a relatively short time. The data supported the hypothesis that supplementation inhibits the late-stage promotion and progression of certain tumors.

In a more recent study on advanced prostate cancer, toenail selenium concentrations (an indicator of long-term selenium intake[25]) were measured in a nested case-control within the Health Professionals Follow Up Study involving 33,737 men.[26] Advanced prostate cancer was noted in 181 patients. The multivariate-adjusted relative risk comparing the highest with the lowest quintile of toenail selenium was 0.35 (95% confidence interval = 0.16-0.78; P for trend = 0.03). Median daily intake of selenium was noted to be 86 mcg among men in the lowest quintile and 159 mcg among those in the highest quintile. This suggests a two-thirds relative reduction in the risk of advanced prostate cancer for men with the highest selenium levels documented. These results are similar to and support those found previously.[13]

The results from these studies have been viewed with caution given the potential risk of selenium toxicity (*see Adverse Effects*) and the scientific risk of using secondary endpoints in randomized trials.[27] Clark et al[13] enrolled few women (25% compared with 75% men) and evidenced no effect on breast cancer, despite animal tumor model studies showing a positive effect.

**Adverse Effects**

Yang et al found no clinical signs of selenium toxicity

## Selenium Among Leading Nutritional Supplements

Visit any vitamin section in the local grocery store or pharmacy and you'll see a wide variety of nutritional supplements and herbal products designed to help people look better, feel healthier, and have more energy. Selenium is likely to be on the shelves. In fact, this mineral ranks as the 10th most popular supplement in the United States, behind vitamin E, ginkgo, chondroitin/glucosamine, calcium with vitamin D, kava, garlic, St. John's wort, and 5HTP, according to a recent consumer survey conducted by NBTY Inc.

In addition to its reputation as a potential cancer preventative, selenium is reported to protect against heart disease, arthritis, and accelerated aging. It may also relieve depression. Articles about these and other benefits of selenium, which takes its name from the Greek word Selênê (moon) for its pasty white color, have been appearing in the popular press recently.

An article in the December 1998 issue of *Natural Health* points out selenium's essential nature. Since the human body does not produce selenium, it must be obtained through diet. The best sources are tuna, king crab, halibut, soybeans, cereal grains, and Brazil nuts. (*See Table 1.*) According to *Natural Health*, experts recommend taking 50-200 mcg of organic forms of the mineral.

Both the July-August and October 1998 issues of *Health* contained articles about selenium offering hope for preventing prostate, lung, and colon cancers. Geographic surveys indicate that people living in regions where the soil is rich in selenium have fewer cancers that people living elsewhere. The magazine suggests that readers speak to their doctors about whether family history or lifestyle habits put them at risk for cancer and whether selenium supplementation is warranted.

*Prevention*'s April 1998 *Consumer's Guide to Supplements* says that although selenium shows great promise in fighting cancer, people with abnormal kidney function should talk to their physician before supplementing with minerals.

In his book *Eight Weeks to Optimum Health*, Andrew Weil recommends taking selenium with vitamin E since they enhance each other's absorption. However, Weil does not recommend taking vitamin C at the same time since some forms of vitamin C and selenium interfere with each other's absorption. ■

at intakes of up to 853 mcg/d, but documented toxicity has been observed in patients taking 1 mg of selenium daily.[12] Selenium intoxication can occur and may include the presence of a garlic odor on the breath, loss of hair and nails, diarrhea, abdominal pain, pulmonary edema, tooth decay, skin lesions on the hands and feet, polyneuropathy, and ultimately death.[12]

Patients known to have hypothyroidism secondary to iodine deficiency should not receive supplemental selenium as this may worsen hypothyroidism.[8]

Clinical signs of selenium deficiency include whitened nail beds.[28] Clinical signs of selenium intoxication include a break on the nail wall. Thumbs are affected first. As new growth continues, the broken nail is pushed forward and drops off. A new nail forms but it is fragile and thickened with a rough surface.[12]

**Selenium may interact with which of the following vitamins:**

a. Vitamin K
b. Vitamin A
c. Vitamin C
d. Vitamin D

## Interactions

Use of inorganic sodium selenite or selenate, as often found in commercial multivitamin supplements, has been noted to interact with ascorbic acid, leading to decreased absorption of selenium.[29] This does not appear to be the case with organic forms of selenium.[29] Selenium levels are also known to be depressed by smoking, alcohol, and oral contraceptives.[30] Vitamin E appears to reduce the oxidative damage seen in selenium deficiency. Therefore, concomitant use, especially in selenium-deficient patients, may be beneficial.[23]

One case report notes selenium supplementation exacerbating hypothyroidism in an iodine-deficient individual.[8] The authors caution that selenium supplementation may aggravate thyroid dysfunction. However, in the United States where iodine deficiency is rare, this likely does not represent a significant problem.

## Formulation

Most multiple vitamin formulations now contain some selenium, most often in the inorganic form and with dosages ranging from 10-100 mcg. It is possible, however, to purchase organic selenium in the form of enriched brewer's yeast in dosages of up to 200 mcg per tablet.

Most dietary selenium is in the organic form. Due to interactions and possible increased toxicity from inorganic use, organic preparations are favored. Studies have used both inorganic and organic forms of selenium.[3,29]

**Table 1. Food Sources of Selenium**

| Food Source | Serving Size | Selenium Content |
|---|---|---|
| Brazil nuts | 1 oz (6-8 kernels) | 839.2 mcg |
| Tuna (light, in water) | 3 oz | 68.3 mcg |
| Alaskan king crab | 1 leg | 53.6 mcg |
| Beef liver | 3 oz | 48.5 mcg |
| Sardines | 3.75 oz can | 48.5 mcg |
| Halibut | 3 oz | 39.8 mcg |
| Skinless chicken breast | 1/2 breast | 23.7 mcg |
| Long-grain brown rice | 1 cup | 19.1 mcg |
| Eggs | 1 hard-boiled | 15.4 mcg |
| Bran bread (wheat, oat, rice) | 1 slice | 7.6-11.2 mcg |
| Mushrooms | 1/2 cup (cooked) | 9.3 mcg |
| Soybeans | 1 cup (cooked) | 2.5 mcg |
| Broccoli | 1/2 cup (cooked) | 1.5 mcg |
| Garlic | 1 clove (raw) | 0.426 mcg |

Source: Online USDA Nutrient Database for Standard Reference

## Dosage

The National Research Council has established the RDI for selenium at 70 mcg/d for men and 55 mcg/d for women.[31] The U.S. Environmental Protection Agency (EPA) has established a reference dose for selenium that represents "an estimate of a daily exposure to the population that is likely to be without an appreciable risk of deleterious effects during a lifetime." This has been estimated to be 350 mcg/d for a 70 kg male.[31]

Many studies reviewed have cited benefit in cancer prevention using 200 mcg/d.

## Dietary Sources

Selenium is found throughout the world in soil and is incorporated into plants and ultimately livestock. Human dietary intake comes from the consumption of bread, cereals, nuts, fish, poultry, and meat.[7] Certain vegetables such as broccoli, mushrooms, and garlic are also important sources.[29] Brazil nuts represent the richest natural source of selenium.[7]

Variation in soil selenium content exists throughout the world, leading to differences in overall dietary intake.[32] Studies have documented low soil concentrations in regions of Europe, Central Africa, and China.[33] In the United States, lower levels have been observed on the east coast and higher levels in the west and midwest, most notably in North and South Dakota.[27] Higher selenium levels tend to be found in less industrialized areas.[23]

## Conclusions

Although overall epidemiological evidence is inconclusive, the results from several recent clinical trials provide compelling evidence to support an inverse relation-

ship between selenium levels and cancer risk. Selenium supplementation in dosages used in the recent literature appear to be safe and possibly effective in lowering the risk of a number of prevalent cancers. The dosages studied are well within safe limits of daily consumption. Questions remain with regard to the degree of benefit in women and to the exact mechanisms of action. In areas in which selenium levels are low, public interest organizations should determine whether selenium supplementation, like fluoride and folic acid supplementation, is in the public's best interest.

**Recommendation**

Supplemental selenium in dosages up to 200 mcg/d in those patients without known contraindications and especially in those at high risk for developing malignancy, particularly lung, colorectal, or prostate cancer, should be considered. Dosages should certainly not exceed 350 mcg/d.[31] Further long-term confirmatory studies and larger randomized, controlled trials will need to extend over long periods of time, involve diverse populations, and use a wide range of selenium dosing. Until then, we believe the promise of supplemental selenium along with its safety at dosages used in recent trials warrant serious consideration for regular use in clinical practice. ❖

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**Vitamin and mineral supplements usually contain selenium in what form?**

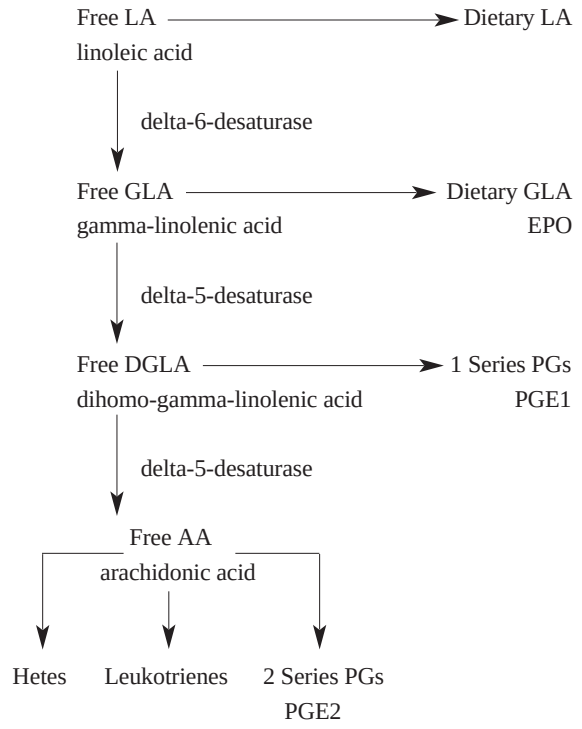
a. Inorganic sodium selenite and selenate
b. Organic selenium-enriched yeast
c. Both organic and inorganic forms are available.
d. Vitamin and mineral supplements usually do not contain selenium.

**References**


1. *Nutrition and Cancer*. Washington, D.C.: National Academy Press; 1982:496.
2. Wattenberg LW. Inhibition of carcinogenesis by minor dietary constituents. *Cancer Res* 1992;52(Supp): 2085s-2091s.
3. Helzlsouer KJ. Selenium and cancer prevention. *Semin Oncol* 1983;10:305-310.
4. Ganther HE. Pathways of selenium metabolism including respiratory excretory products. *J Am Coll Toxicology* 1986;5:1-5.
5. Ip C, et al. Potential of food modification in cancer prevention. *Cancer Res*(Suppl) 1994;S4:1957s-1959s.
6. Ip C, Ganther HE. Relationship between the chemical form of selenium and anticarcinogenic activity. In: *Cancer Chemoprevention*. Boca Raton, FL: CRC Press; 1992:479-488.
7. Rayman MP. Dietary selenium: Time to act. *BMJ* 1997;314:387-388.
8. Hofbauer LC, et al. Selenium-induced thyroid dysfunction. *Postgrad Med J* 1997;73:103-104.
9. Diplock AT. Antioxidants and disease prevention. *Mol Aspects Med* 1994;15:293-376.
10. Marshall MV, et al. Selenium effects on the carcinogenicity and metabolism of 2-acetylaminofluorine. *Cancer Lett* 1979;7:331-338.
11. Spallholz JE, et al. Injectable selenium: Effect on the primary response of mice. *Proc Soc Exp Biol Med* 1975;148:37-40.
12. Yang G, et al. Endemic selenium intoxication of humans in China. *Am J Clin Nutr* 1983;37:872-881.
13. Clark LC, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. *JAMA* 1996;276:1957-1963.
14. Clayton C, et al. Diet and azo dye tumors: Effect of diet during a period when the drug is not fed. *Cancer Res* 1949;9:575.
15. Thompson HJ, et al. Selenium inhibition of N-methyl-N-nitrosurea-induced mammary carcinogenesis in the rat. *J Nat Cancer Inst* 1980;65:1299-1301.
16. Jacobs MM, et al. Inhibitory effects of selenium on 1,2-dimethylhydrazine and methylazoxymethanol acetate induction of colon tumors. *Cancer Lett* 1977;2:133-137.
17. Harr JR, et al. Relationship of dietary selenium concentration; chemical cancer induction; and tissue concentration of selenium in rats. *Clin Toxicol* 1973;6: 487-495.
18. Shamberger RJ, Frost DV. Possible protective effect of selenium against human cancer. *Can Med Assoc J* 1969;100:682.
19. Schauzer GN, et al. Cancer mortality correlation studies, III *Bioinorganic Chem* 1977;7:23-34.
20. Clark LC, et al. Selenium in forage crops and cancer mortality in US counties. *Arch Environ Health* 1991;46:37-42.
21. McConnell KP, et al. The relationship of dietary selenium and breast cancer. *J Surg Oncol* 1980;15:67-70.
22. Shamberger RJ, et al. Antioxidants and cancer. I. Selenium in the blood of normals and cancer patients. *J Nat Cancer Inst* 1973;50:867-870.
23. Willett WC, et al. Prediagnostic serum selenium and risk of cancer. *Lancet* 1983;2:130-134
24. Menkes MS, et al. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. *N Engl J Med* 1986;315:1250-1254.

25. Ovaskainen ML, et al. Toenail selenium as an indicator of selenium intake among middle-aged men in an area with low soil selenium. *Am J Clin Nutr* 1993:57:662-5.
26. Yoshizawa K, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998;90:1219-1224.
27. Colditz GA. Selenium and cancer prevention. Promising results indicate further trials required. *JAMA* 1996;276:1984-1985.
28. Abrams CK, et al. Selenium deficiency in long-term total parenteral nutrition. *Nutr Clin Prac* 1992;7: 175-178.
29. Hendler SS. Selenium. In: *The Doctors' Vitamin and Mineral Encyclopedia*, 1st ed. New York, NY: Fireside Publishing; 1991:183-193.
30. Burney PG, et al. Serologic precursors of cancer: Serum micronutrients and the subsequent risk of pancreatic cancer. *Am J Clin Nutr* 1989;49:895-900.
31. Levander OA, et al. Deliberations and evaluations of the approaches, endpoints and paradigms for selenium and iodine dietary recommendations. *J Nutr* (Suppl) 1996:2427s-2434s.
32. Shamberger RJ, Willis CE. Selenium distribution and human cancer mortality. *CRC Crit Rev Clin Lab Sci* 1971;2:211-221.
33. Moreno-Reyes R, et al. Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. *N Engl J Med* 1998;339:1112-1120.

**Figure 1. Metabolic Pathways of Essential Fatty Acids**




Adapted from Horrobin DF, et al. *Hypotheses* 1979;5:969-985.

# Evening Primrose Oil in the Treatment of Atopic and Irritant Contact Dermatitis

*By David Schiedermayer, MD*

WHEN I EXAMINE PATIENTS' HANDS, I LEARN ABOUT their interaction with the world. Farmers have hypertrophied interosseous muscles and pole-sized wrists. Anxious patients have chewed nails, or worse yet, gnawed-on cuticles. Mechanics have deeply oil-stained fingers. Unlucky or careless laborers have missing digits.

But the main cause of occupational skin disease is irritant contact dermatitis (ICD), which I've seen in shoemakers, homemakers, and doctors. Atopic dermatitis (AD) has some pathophysiological similarities to ICD, but often presents without any known external chemical irritation. AD is a genetically determined condition readily worsened by seasonal flare, infections, and food allergies.[1]

## Pathophysiology

In dermatitis, irrespective of cause, the outer layer of the stratum corneum is structurally and functionally altered; its usual impermeable nature is impaired. Substances that irritate it are able to cross into the dermis unimpeded. The theory behind treatment is to restore the impermeable nature of the barrier through restoring some of the fatty acids present in the skin. Gamma linolenic acid (GLA) is one such fatty acid. It is essential for production of prostaglandins, prostacyclins, thromboxanes, and leukotrienes. A deficiency can lead to hyperproliferative changes and scaliness.

## Derivation

Many different strains of evening primrose (*Oenothera biennis*) are found in nature and under cultivation. The seed oil, which is a typical vegetable oil, varies considerably in the concentration of the essential/n6 fatty acid GLA, the active ingredient in evening primrose oil (EPO).

Epogam, one commercially available source of EPO, has seed oil derived from four flower strains that have been selected and bred to yield oil of constant composition.[2]

### Metabolism

In healthy volunteers with no dermatological symptoms who received six capsules of Epogam, there was significant individual variation in absorption and elimination of GLA from the serum. However, on average, the maximal concentration was about 4.5 times higher than the concentration in volunteers not taking Epogam. Other fatty acid metabolites showed no significant changes in serum concentrations. The uptake of GLA from the GI tract was much slower in the morning than in the evening. About 12 hours after administration of six capsules, serum levels returned to baseline.[3]

### Proposed Mechanism of Action

Some authors hypothesize that patients with ICD or AD have defective functioning of the enzyme that desaturates linoleic acid, delta-6-desaturase. Without this enzyme, prostacyclins, thromboxanes, and leukotrienes cannot be produced from this pathway. Figure 1 shows arachidonic acid as the substrate for the formation of prostaglandin E2, and DGLA as the substrate for prostaglandin E1 formation.[4]

### Clinical Studies

A meta-analysis of placebo-controlled studies of the efficacy of Epogam, published by the manufacturer's research institute, showed that in four controlled parallel designed trials, both patient and doctor scores showed a highly significant improvement over baseline. In the crossover trials, however, doctors' ratings failed to achieve significance. When the results were related to changes in plasma levels of DGLA and arachidonic acid levels, there was a positive correlation between improvement in clinical score and rise in serum fatty acid levels. The researchers hypothesized that a rise in arachidonic acid as well as DGLA may reflect conservation of arachidonic acid in the lipid fraction and phospholipids of the skin.[2] Unfortunately, insufficient detail of prior unpublished studies used in the analysis is provided, and this "meta-analysis" appears incomplete.

When EPO (Epogam) was evaluated in a double-blind, placebo-controlled trial of 39 patients with chronic (greater than one year) stable hand dermatitis, the findings were not as encouraging. Active therapy with 600 mg/d of GLA (twelve 500 mg capsules of Epogam containing 50 mg of GLA) was administered orally to the study group for 16 weeks with another eight weeks of continued observation. Patients were assessed clinically, using a visual analogue scale at four-week intervals. Plasma and red blood cell lipograms, as well as skin biopsies, were taken before therapy, after the 16-week supplementation, and at week 24.

Improvements in clinical parameters were present in both the Epogam and placebo groups, but no statistical difference could be confirmed. Regular follow-up visits made the patients more aware of their condition and clinical guidance could have enhanced the use of emollients and avoidance of allergens. CBC and epidermal biochemistry were normal at baseline. No change in the lipid composition of plasma red cells or epidermis could be detected during the trial. The authors concluded that orally administered GLA for chronic hand dermatitis is not superior to placebo.[5]

The best study was a double-blind, placebo-controlled, parallel group study done to avoid the methodological and analytic problems of previous studies.[6] Patients were randomized to receive EPO, EPO and fish oil, or placebo for 16 weeks. Of 123 subjects recruited, 102 completed the treatment period. No improvement with any active treatment was demonstrated. This study combined n6 (EPO) and n3 essential fatty acids (fish oil), analyzed the two groups together, and still showed no positive effect.

### Adverse Effects

Adverse effects included nausea, indigestion, headaches, and softened stools but no serious adverse effect has been reported.[7] Weight gain is possible if large doses are taken. One observer warns of a potential risk of inflammation, thrombosis, and immunosuppression from slow accumulation of tissue arachidonate after use of GLA for more than one year.[8]

Administration of EPO is considered as safe as the administration of corn oil.[9] Effects on serum cholesterol, HDL, and LDL fractions are not evaluated in most studies, but should be evaluated to define potentially adverse effects of EPO on the lipid profile. EPO studies in rats, mice, and dogs do not support the hypothesis that linoleic acid initiates or promotes tumor formation.

**The largest trial of evening primrose oil, a double-blind, crossover design with random assignment of 123 patients to treatment groups showed:**

a. No difference between evening primrose oil and placebo in erythema, scale, excoriation, lichenification, or overall severity.
b. The ease of documenting compliance.
c. Elevated blood levels correlating with effects
d. Marked diminution in rash.

### Current Clinical Therapy

Current therapeutic options for both ICD and AD are limited; the only generally accepted therapy is avoiding

irritants for as long as the skin is not completely healed. The benefit of topical corticosteroids is controversial. Steroids are believed to act, at least in part, by reducing the mobilization of arachidonic acid from phospholipid stores and decreasing the availability of free arachidonic acid for conversion to pro-inflammatory metabolites.[2] However, clinical trials are notoriously difficult to perform, because of the inherent variability of the clinical state, the subjective nature of the assessment, and a large placebo response.[2]

Other treatments include emollients, antihistamines, ultraviolet B, psoralen plus ultraviolet A, Chinese herbs, and cyclosporin.

### Drug Interactions

EPO should not be used with anticonvulsants because it may lower the seizure threshold.[10]

### Formulations and Dosing

Epogam contains 320 mg of linoleic acid and 40 mg of GLA as well as trace amounts of palmitic, oleic, and stearic acid, and added vitamin E as an antioxidant. Efamol is 72% linoleic acid, 12% oleic acid, and has 45 mg of GLA per capsule. In most studies, subjects took 10-12 capsules per day.

### Conclusion

The claim that Epogam produces "a substantial and highly significant clinical improvement" in AD or ICD appears exaggerated. Epogam is no more effective than placebo in a good clinical trial.

Many of the trials to date that suggest an effect have been crossover studies in small number of patients. The long duration of treatment, the variable natural courses of the disease in question, the placebo effect, and publication bias (nearly all trials so far have been sponsored by the same company) suggest the need to take any purported effect with some caution.[11] Further rigorous trials of both GLA and EPO are warranted.[12]

### Recommendation

At present, EPO is best regarded only as an optional addition to existing treatment for ICD or AD, and as a dietary fatty acid supplement rather than a medication. It is no more effective than placebo and is also expensive.[8] Many unanswered questions remain about the optimal dose and duration of treatment. It does appear to be a relatively harmless substance. ❖

**Research on EPO is difficult because:**

a. No foundations are interested in providing funding.
b. The duration of treatment must be long.
c. The diseases have standard natural courses.
d. The placebo effect is not significant.

### References


1. Meneghini CL, Bonifazi E. Correlation between clinical and immunological findings in atopic dermatitis. *Acta Derm Venereol* (Stockh) 1985;114:140-142.
2. Morse PF, et al. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema: Relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989;121:75-90.
3. Martens-Lobenhoffer JM, Meyer FP. Pharmacokinetic data of gamma-linolenic acid in healthy volunteers after the administration of evening primrose oil (Epogam). *Inter J Clin Pharmacol Ther* 1998;36: 363-366.
4. Wright S. Atopic dermatitis and essential fatty acids: A biochemical basis for atopy? *Acta Derm Venereol* (Stockh) 1985;114:143-145.
5. Whitaker DK, et al. Evening primrose oil (Epogam) in the treatment of chronic hand dermatitis: Disappointing therapeutic results. *Dermatology* 1996;193:115-120.
6. Berth-Jones J, Graham-Brown RAC. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993;341:1557-1560.
7. Anonymous. Gamolenic acid in atopic eczema: Epogam. *Drug Ther Bull* 1990;28:69-70.
8. Phinney S. Potential risk of prolonged gamma-linolenic acid use. *Ann Intern Med* 1994;120:692.
9. Everett DJ, et al. Chronic toxicity studies of Efamol evening primrose oil in rats and dogs. *Med Sci Res* 1988;16:865-866.
10. Miller LG. Herbal medicinals: Selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200-2211.
11 Goonaratna C. Good morning, evening primrose oil. *Ceylon Med J* 1995;40:132-133.
12. Kleijnen J. Evening primrose oil: Currently used in many conditions with little justification. *BMJ* 1994;309:824-825.


## Review of Herb-Drug Interactions

**Source:** Miller LG. Herbal medicinals: Selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200-2211.

*With Comments from John La Puma, MD, FACP*

HERBAL MEDICINALS ARE BEING USED by an increasing number of patients who typically do not advise their clinicians of current use. Known or potential drug-herb interactions exist and should be screened for. For example, feverfew, garlic, ginkgo, ginger, and ginseng may alter bleeding time and should not be used concomitantly with warfarin sodium. Ginseng should not be used with estrogens or corticosteroids because of possible additive effects. Valerian should not be used with barbiturates because excessive sedation may occur. Kava when used with alprazolam has resulted in coma.

### Comment

In this unusual review article, PharmD Miller catalogs commonly used herbal medicinals and associated drug-herb interactions, both theoretical and actual. She first briefly recounts evidence for the effectiveness of chamomile, echinacea, feverfew, garlic, ginger, ginkgo, ginseng, saw palmetto, St. John's wort, and valerian. She then identifies drugs with a narrow therapeutic window and several herbal interactions with them. Finally, she lists more drugs, herbs, and minerals "with known or potential drug-herb interactions with commonly used herbal medicinals."

This article reads like an impatient life sciences catalog: Dr. Miller has a lot of information and wants to get it all out. But it's often difficult to differentiate between basic science and clinical cases without referring to the 171 references, which are largely bench laboratory observations and single case reports.

So, this potentially critical article is not well-organized or easy to use—except for the Summary Table of Drug-Herb Interactions of Commonly Used Drugs. Worth review, even with a great deal of room for improvement, the table lists actual and potential herbal interactions with, among others, diuretics (dandelion, uva-ursi, gossypol), hypoglycemics (chromium, karela), iron (chamomile, feverfew, St. John's wort) levothyroxine (kelp, horseradish), NSAIDs (gossypol, uva-ursi), phenobarbital (wormwood, sage, evening primrose oil, borage), phenytoin (see phenobarb), and spironolactone (licorice).

### Recommendation

Regard most of the data here with a grain of salt, but review the table noted above on page 2205; it is currently the best of its kind that I know of in the peer-reviewed medical literature. ❖

## Yoga for Carpal Tunnel Syndrome

**Source:** Garfinkel MS, et al. Yoga-based intervention for carpal tunnel syndrome: A randomized clinical trial. *JAMA* 1998; 280:1601-1603.

TO DETERMINE THE EFFECTIVENESS OF a yoga-based regimen for relieving symptoms of carpal tunnel syndrome, we randomized 42 employed or retired individuals with carpal tunnel syndrome (median age 52 years) to either current treatment, including a wrist splint, or a twice weekly yoga-based intervention. The intervention consisted of 11 yoga postures designed for strengthening, stretching, and balancing each joint in the upper body along with relaxation, and lasted 1-1.5 hours weekly.

Subjects in the yoga groups had significant improvement in grip strength (increased from 162 mm to 187 mm Hg; P = 0.009) and pain reduction (decreased from 5.0 mm to 2.9 mm; P = 0.02), but changes in grip strength and pain were not significant for controls. The yoga group had significantly more improvement in Phalen's sign (12 improved vs. 2 in control group; P = 0.008), but no significant differences were found in sleep disturbance, Tinel's sign, and median nerve motor and sensory conduction time.

We conclude that a yoga-based regimen was more effective than wrist splinting or no treatment in relieving some symptoms and signs of carpal tunnel syndrome.

### Comment

A major cause of lost work days and wages, carpal tunnel syndrome is hard to treat. Many patients are reluctant to undergo surgery; many insurers are reluctant to pay for operations unless splints have been worn and nerve conduction velocities have slowed markedly.

In an industrial site and a geriatric clinic, these Penn investigators asked all enrolled subjects not to change medicines or job responsibilities during the study. Inclusion criteria included delayed median nerve conduction latencies; exclusion criteria included systemic disease as an etiology.

The investigators used "the Ijengar approach to hatha yoga, which emphasizes proper structural alignment of the body." The 11 postures are held for 30 seconds each and then repeated.

The postures are sitting with extension of the trunk; hands in prayer position, arms extended overhead; arms extended overhead with fingers interlocked; arms interlocked in front of the body; chair twists; standing, mountain pose; 90-degree forward bend to wall; arms extended overhead with palms together in prayer position; dog pose with chair; hands joined in prayer position behind the back; relaxation.

Why might carpal tunnel respond to yoga? These investigators postulate "...stretching may relieve compression in the carpal tunnel, better joint posture may decrease intermittent compression, and blood flow may be improved to decrease ischemic effects on the median nerve."

Methodological problems are evident in this preliminary communication. Though 42 of the 51 randomized subjects finished the trial, for example, the data are too few to analyze in detail. The subjects' analgesic regimen was neither studied nor optimized. There was no assessment of adherence with yoga or with the splint; there was no follow up; there were no reasons given for dropouts.

There were also no complications reported. This type of yoga, believed to improve strength, coordination, and flexibility, has little, if any, morbidity.

### Recommendation

Yoga may improve the pain of carpal tunnel syndrome, with almost no risk. Consider it for patients who reject splints, who have trouble with nonsteroidals, or who want to delay surgery and will practice conscientiously. ❖

## Neurotoxicity from Whole St. John's Wort

**Source:** Bove GM. Acute neuropathy after exposure to sun in a patient treated with St. John's wort. *Lancet* 1998; 352:1121-1122.

A 35-YEAR-OLD WOMAN TOOK GROUND whole St. John's wort (500 mg/d) for mild depression, after reading a magazine article. After 4 weeks, she developed stinging pain on her face and dorsum of both hands (areas exposed to the sun). Spontaneous pain was mild but worsened during and after being in the sun. Pain was provoked by minimal mechanical stimuli such as light touch or air movement. Cooling increased and warming decreased the pain. She sought help when the same symptoms developed on her arms and legs a few hours after sunbathing, and were limited to the exposed skin.

Examination two weeks after the pain started revealed allodynia but no skin burns, or other motor or sensory changes. Brushing lightly, blowing air, and cold temperature exacerbated the pain. Three weeks after discontinuation of the botanical, the symptoms began to improve, and gradually disappeared over the next two months.

The patient's symptoms were consistent with demyelination of cutaneous axons. Photoactive hypericins produce cytotoxic singlet oxygen and free radicals when exposed to light. Lipid peroxidation occurs as a result, and myelin may suffer.

### Comment

St. John's wort seems ubiquitous. In 1997 U.S. sales topped $47 million. Robert's Potato Chips now come laced with the stuff. So do new Celestial Seasonings teas (drink 36 cups, get 900 mg of something). A division of Boehringer Ingelheim Pharmaceuticals is promoting a brand. And Germany had, as of 1995, 18 single-herb hypericum products. Is it in the water, as Walker Percy feared? And how much can harm you?

This patient apparently ingested St. John's wort's ground yellow, star-shaped flowers and buds. Grazing animals, especially cows and sheep, have had phototoxic reactions to the same whole flower preparation. The species used to make the medication is just one of 378 known. The author, from Boston's Beth Israel Deaconess, references a report of photosensitivity and pigment changes after St. John's wort ingestion in humans.

St. John's wort photosensitization is dose-related, and has occurred with plasma concentrations of 50 mcg of hypericin per ml, according to Schulz' Rational Phytotherapy—six orders of magnitude above what patients who take an extract of 300 mg of 0.6% hypericin tid should have.

Typically, of course, patients do take extracts. In *Alternative Medicine Alert* (1998;1:6) Hornig reports: "Side effects are infrequent and typically mild. The overall incidence of side effects in the 23 studies included in the meta-analysis (of 23 studies) by Linde et al was 19.8% for hypericum compared with 52.8% for standard antidepressant therapy (*BMJ* 1996; 313:253-258.) ... The most common side effects of the herbal extract [administered at the suggested dosage] include dry mouth, dizziness, gastrointestinal complaints (most commonly constipation) and confusion."

### Recommendation

Ask patients not to make their own teas, powders, brownies, or anything else from whole St. John's wort. There's no telling what they're getting, and free radical damage and neurotoxicity are real possibilities. ❖



In Future Issues:

Bilberry for Vision
Acupuncture for Narcotic Addiction
Peppermint Oil for Irritable Bowel Syndrome