The Physicians’ Health Study II
Or
How To Make Vitamins C and E Not Prevent Heart Disease

I am a Doctor of Oriental Medicine with a strong interest in nutritional treatment/prevention strategies for many “modern” diseases, such as heart disease, osteoporosis, cancer, AIDS, etc. Therefore, I am always looking into medical research that concerns vitamin/mineral supplements.

The Physicians’ Health Study II recently published results on supplemental vitamin C and vitamin E used to prevent heart disease. The study ran for 10 years and enrolled over 14,000 physicians into the study. The major conclusions of the study were that neither vitamin C nor vitamin E did anything to prevent heart disease. 1

I decided that I needed to look at this study more closely.

First, here’s some background information about vitamin E.

**What is Vitamin E?**

Vitamin E has 9 major chemical forms. They are:

- d-alpha-tocopherol
- d-beta-tocopherol
- d-gamma-tocopherol
- d-delta-tocopherol
- alpha-tocotrienol
- beta-tocotrienol
- gamma-tocotrienol
- delta-tocotrienol

dl-alpha-tocopherol (synthetic vitamin E)

In addition, there are “suffixes” that can be added to some of these forms. For example, d-alpha-tocopherol-acetate. In this discussion, my purpose is best served by ignoring the suffixes.

**Synthetic Vitamin E**

When alpha-tocopherol is produced synthetically, you end up with a form that can be called dl-alpha-tocopherol. In scientific journals, it might also be called all-rac-alpha-tocopherol. This would be a ninth type of vitamin E. Because it is synthetic, it is the least expensive and the most common.
Carbon tends to want to share 4 electrons, and therefore form 4 bonds. Frequently, the sequence of the last 3 bonds makes a significant difference in the properties of the resulting chemical even though the chemical formula may be identical. These sequences are usually described as either right-handed (d- or R-) or left-handed (l- or S-).

Vitamin E has three locations where the sequence of what the carbon is bonding to makes a significant difference in the function of the vitamin E. Naturally-occurring alpha-tocopherol would be correctly labeled RRR-alpha-tocopherol. This is the form of alpha-tocopherol that our bodies are used to, and so this is the optimal way to deliver this form of vitamin E. When alpha-tocopherol is synthesized, the right-handedness or left-handedness is random at all three locations. This is what results:

RRR-alpha-tocopherol
RRS-alpha-tocopherol
RSR-alpha-tocopherol
RSS-alpha-tocopherol
SRR-alpha-tocopherol
SRS-alpha-tocopherol
SSR-alpha-tocopherol
SSS-alpha-tocopherol

Because these occur randomly, they also occur in roughly equal amounts. Therefore, only 1/8th of the synthetic alpha-tocopherol matches the “natural” alpha-tocopherol. All the other types have significant potential for functional differences between them and the natural alpha tocopherol, and may be worthless for some purposes where RRR-alpha-tocopherol would be perfectly well suited. I usually summarize this for my patients by telling them that the synthetic dl-alpha tocopherol is 7/8ths “plastic garbage” that needs to be removed from the body.

Nine Chemical Names, Nine Different Effects?

It is merely a quirk of how vitamins are named that the four tocopherols, the four tocoptrienols, and dl-alpha-tocopherol are all called “vitamin E”. They are distinct chemicals, and although related, are known to have different chemical properties. Gamma-tocopherol occurs in the greatest quantities in food, and it is expected to be in the highest quantities in human tissue in a healthy person.

The most common supplement form of vitamin E that is available from reputable health-food stores is the pure d-alpha-tocopherol form (let’s presume that we are making an intelligent choice here, and have ruled out the use of the synthetic version). All forms of vitamin E displace each other. Therefore, the result of taking the most commonly available “natural” vitamin E supplements will be an increase in the levels of alphatocopherol and a REDUCTION in the levels of all other forms of vitamin E.

The differing functions of the 8 types of natural types of vitamin E are not well studied, and are only recently being discovered. The published report from the Physicians’ Health
Study states - … the gamma-tocopherol isomer also may have a role in cardiovascular disease prevention because it has a greater efficacy than alpha-tocopherol to inhibit lipid peroxidation and it may be suppressed in the presence of alpha-tocopherol. 2

If you have computer access to the internet, I suggest that you search for:

tocotrienols cancer
tocotrienols breast cancer
tocotrienols heart disease

Each of these searches will generate a significant number of articles. Looking through them should be enough to steer you to the conclusion that tocotrienols are something you should be getting regularly.

The Vitamin E That The Physicians’ Health Study Chose

So, what kind of vitamin E did the Physicians’ Health Study II choose? They chose dl-alpha tocopherol – the least effective variety with the most chance for adverse effects. 2

Now Look At Vitamin C

The Physicians’ Health Study chose to use 500 mg tablets of synthetic ascorbic acid. Let’s see how intelligent their choice was for this vitamin. 2

Synthetic ascorbic acid is a 50-50 mixture of D-ascorbic acid and L-ascorbic acid. The “L” variety is what occurs in nature, and this is usable vitamin C. The “D” variety is excreted unused. 3 So, their true dosage of “vitamin C” is now down to 250 mg.

Vitamin C is an unstable molecule. Its rate of decay will be accelerated by the presence of heat, light, and oxygen. Vitamin C does not “age” well. 3

The initial distribution of PHS II supplement packages were for a 6-month period. Thereafter, the packages were delivered once per year. This means that some aging-related decay of the vitamin C would occur. I have found a wide variety of statements about what the “shelf-life” of vitamin C is, and very few statements about the percentage of loss over time. Therefore, I am guessing when I say that a vitamin C tablet stored at “room temperature” might lose 15% of its’ ascorbic acid over a year, resulting in an average loss of 7.5%.

Also, the vitamin C used was a tablet. The process of making a tablet involves enough pressure to generate some heat, and the added heat will damage a little bit more of the vitamin C. Also, tablets are the most detrimental to the absorption process, sometimes being passed through the digestive tract whole.
So, when all of this is taken into account, what’s the average amount of vitamin C per day? My best guess is about 220 mg.

**Now Compare To Wholistic Recommendations for Treatment/Prevention of Heart Disease**

I have come to quoting vitamin E dosages in milligrams (mg) instead of IU’s. International Units were based upon their ability to increase fertility, and d-alpha tocopherol appeared to accomplish this best. But this is only one of the many benefits that can be derived from a full vitamin E complex, so it is best to give dosages by weight and pay attention to distribution of the various types of vitamin E.

The dosage of vitamin E in this study was 400 IU every other day, which I will re-state as 200 IU / day. The 200 IU’s of synthetic alpha-tocopherol would be 200 mg. My usual recommendations of vitamin E for prevention are around 400 mg/day of a full-spectrum vitamin E (all 4 tocopherols and all 4 tocotrienols). For treatment of an advanced case of heart disease, I increase that recommendation to at least 600 mg/day. Most full-spectrum vitamin E gel-caps are about 400 mg.

Because the 200 mg of vitamin E used in the study is synthetic, only 1/8th of it is natural alpha-tocopherol. This brings down the dosage of “fully-effective” vitamin E down to 25 mg. Some of the functions of vitamin E will be not be well addressed because only 1 of the 8 types of vitamin E are supplemented. Furthermore, the functions not addressed will be actually suppressed because the different types of vitamin E compete with each other, so the levels of the types of vitamin E not supplemented will be driven down further by this unbalanced supplementation.

The net result is that the PHS II supplementation if vitamin E is less than 1/16th of what I usually recommend, and has the capability of causing mild detrimental effects by inhibiting 7 of the 8 types of natural vitamin E.

I usually recommend at least 3 grams per day of vitamin C as a heart-disease preventative and 6 grams per day as part of a treatment. The vitamin C that I recommend is a purified L-ascorbic acid, so it contains no useless D-ascorbic acid. My vitamin C is also subject to gradual decay, but because my vitamin C gets shipped to me monthly, mine looses very little. So the 3 grams probably ends up being 2.9 grams and the 6 grams ends up really being 5.8 grams.

The net result is that the vitamin C that I recommend for heart disease prevention is a dosage of more than 13 times as much as is being used in the PHS II.
Why Did PHS II Make Such Peculiar Choices of Vitamin C and E?

I have been following large-scale studies of vitamin and mineral supplements for several years, and I can tell you that these kind of “unfortunate” choices are made all the time. The information about the 8 kinds of naturally-occurring vitamin E has been available for decades. The information about how to prevent/reverse heart disease with vitamin C and a small collection of other nutrients has been around since the 1950’s and was championed by a two-time winner of the Nobel Prize - Linus Pauling.  

The people who design these studies are neither stupid nor careless. They are PhD’s and MD’s who are being paid very well to design and administer these studies. PHS II cost 114 million dollars (so far).

When I read study reviews on the internet, there is commonly a place for comments at the bottom. Many times, I have seen comments posted that ask questions such as:

- What form of vitamin E are they using? (If they didn’t specify in the review)
- Why are they using synthetic vitamin E?
- Why aren’t they using mixed tocopherols?
- Why aren’t they including tocotrienols?

In almost all cases, the person posting these questions have no apparent medical/scientific background. So, we are led to believe that understanding the virtues of the 8 types of naturally-occurring vitamin E is not allowed in MD’s and research scientists, but is only possible for plumbers, elementary school teachers, receptionists, etc.

Of course, a better explanation comes from looking at who is funding these studies. In the case of PHS II, the funding came from the Nation Institutes of Health (NIH), BASF, Wyeth Pharmaceuticals, and Roche Vitamins, a subsidiary of the pharmaceutical giant of the same name. In 2003, about halfway through the study, Roche sold Roche Vitamins to DSM Nutritional Products Inc. Both the vitamin E and the vitamin C were provided by BASF.

Wyeth and Roche are clearly pharmaceutical giants. BASF was also a pharmaceutical giant at the beginning of the study, but sold that section of the company in 2000 to Novartis. You might ask – Why was big pharma funding studies on nutritional supplements? All of these companies sold some nutritional supplements, but they all had a lot of pharmaceutical profits to lose if the study showed that vitamin C and E prevented heart disease. Pharmaceutical companies make their money selling drugs, which are orders of magnitude more profitable than selling nutritional supplements. It serves their financial interest to see nutritional supplements discredited.

Conflicts of Interest
Conflicts of interest are rampant in the medical-research industry. The authors of the PHS II study reported financial ties with the following pharmaceutical firms:

- Amgen
- Astra-Zeneca
- BASF
- Bayer
- Bristol-Meyers Squibb
- McNeil Consumer & Specialty Pharmaceuticals
- Merck
- Pfizer
- Roche
- Wyeth

On the side on nutritional supplements, funding was reported from the “Natural Source Vitamin E Association”, an organization whose website has a Washington DC address and appears to have only marginal connections to vitamin E.

**Certainly the NIH Is Above All of This?**

But What about NIH? They are, in theory, an unbiased arm of the federal government that should be able to reign in the shenanigans that the pharmaceutical sector might try. Unfortunately, this is not the case. The NIH is yet another area of government that big pharma has figured out how to “buy”.

Dr. Thomas Walsh and Dr. P. Trey Sunderland III are two names of prominent NIH officials caught engaging in grotesque conflicts of interest that probably should have qualified as “racketeering”. Together, they took over $400,000 from drug companies while they were supervising research that related directly back to the source companies. Though there were multiple breaches of existing regulations, and howling breaches of ethical conduct, the NIH took no disciplinary action.

NIH officials found that Walsh took $100,970 from pharmaceutical and biotech companies between 1999 and 2004, while simultaneously leading government-sponsored research of some of the contributing companies' drugs. Walsh was found to have taken fees from both Merck Co. and Pfizer Inc. The NIH review found Walsh had taken $3,000 to attend Merck-sponsored events in 2000 and 2001, while he was leading a "research and development agreement" between Merck and the NIH.

"The review panel finds that the scientific subject matter of the activities overlap directly with Dr. Walsh's research at NIH," wrote Holly Beckerman Jaffe, chief ethics lawyer for the NIH.

A couple years ago, two congressmen on powerful committees switched sides shortly after they launched investigations into conflicts of interest between drug companies and
employees at the NIH.

Representative, WJ "Billy" Tauzin (R-La), was chairman of the House Energy and Commerce Committee, and had cited "secret consulting fees and stock options from drug companies" as reasons to request documentation of all payments from Big Pharma to NIH scientists.

But next thing you know, Tauzin announces that he is not running for reelection, and leaves Congress to become President of the Pharmaceutical Research and Manufacturers of America, the giant trade group that represents Big Pharma, with a reported $2 million a year in salary, benefits and perks.

Next up to bat, was Representative James Greenwood (R-Pa), who led 3 hearings on NIH conflicts of interest and criticized the agency for allowing scientists to use "a swivel chair" to make decisions while taking drug company money.

But low and behold, shortly thereafter, in July 2004, Rep Greenwood announced that he was giving up his post as chairman of the Energy and Commerce subcommittee to retire, only to become President of the Biotechnology Industry Organization, a group that in the same year, urged lawmakers NOT to bar NIH scientists from entering into paid consulting deals.

A third point may make this topic even clearer. In 2002, the Vitamin C Foundation submitted a study proposal to the NIH designed to test the vitamin C/vitamin E/heart disease nutritional therapy recommended by Linus Pauling (2-time Nobel Prizewinner). It was an inexpensive study, costing around $375,000 (about 3% or the current cost of PHS II), and the NIH found no problems in the study design. However, the study was rejected because the NIH “did not feel comfortable with the people running the study”.

Conclusions

I have three concluding statements to make for this article:

1. The PHS II study was “designed to fail”.
2. The NIH is essentially controlled by big Pharma.
3. The funders of PHS II wanted to discredit nutritional supplements most likely because the pharmaceutical companies are feeling threatened by the success of inexpensive nutritional cures of common diseases (for example, heart disease).

Homework?

I like to give “homework” to people who attend my presentations and/or read my articles. No article is so complete that it really “finishes” a subject and no topic is a dead end.
Here are some other related thoughts. I hope that readers will investigate them on their own.

1. Especially at the highest levels, medical research “outcomes” are currently for sale to the highest bidder, and the highest bidder is usually a large pharmaceutical company. The kind of sleight-of-hand, dubious study design, extraordinary conflicts of interest, and outrageous unethical behavior detailed here is not unique to PHS II. You could probably find the equivalent or worse in many current peer-reviewed studies involving drugs and nutritional supplements.

A good way to start looking into this might be to do a computer search on “medical research fraud”

2. Vitamin C and vitamin E, if used in adequate doses, and when care is taken to avoid ineffective forms, produce very favorable results in the prevention of heart disease. Just in case you were wondering, the proper C and E that I have referred to (along with a few more supplements), in the proper dosages produces consistently excellent results with my patients.

A good way to start looking into this is to go to http://www.vitamincfoundation.org/vitcheart.htm

About the Author

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Footnotes:


2. Journal of the American Medical Association, Vitamins E and C in the Prevention of Cardiovascular Disease in Men http://jama.ama-assn.org/cgi/content/full/300/18/2123

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   http://www.internetwks.com/owen/suppress.htm

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   http://phs.bwh.harvard.edu/faqs.htm

7. Roche Media Release, Roche completes exit from vitamins business
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8. FoodNavigator.com, Novartis buys BASF phamaceuticals

9. Pringle, Evelyn, Big Pharma Research Racket Is Killing People
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10. Vitamin C Foundation’s NCCAM Grant Request Page
    http://vitamincfoundation.org/NCCAMgrant/