

Are Antioxidants Bad for Us?

A Response to Dr. Paul Offit

In a recent essay in the New York Times, Dr. Paul Offit correctly notes that several large controlled clinical studies evaluating the impact of supplementation with the antioxidants vitamin E and beta carotene have had adverse health outcomes. (He might also have mentioned that vitamin E supplementation slightly increased the risk of prostate cancer in a recent study.) From this, he draws the conclusion that antioxidant supplementation *per se* seems to be inadvisable.

In fact, the notion that antioxidant supplementation is inherently bad is superficial and unjustified. The reason why various antioxidant supplements have been evaluated for their health effects is that evidence is overwhelming, both from animal studies and clinical evaluations, that excessive oxidative stress – the metabolic phenomenon which antioxidants help to control - is a key driver of many of the disorders which commonly afflict us. Atherosclerosis is clearly associated with and promoted by oxidative stress; oxidants play a key role in the tissue damage inflicted by heart attack and stroke; the complications of diabetes are largely driven by oxidative stress; oxidative stress can promote the DNA mutations that give rise to cancers in chronically inflamed tissues; the inflammation associated with rheumatoid arthritis and other autoimmune disorders is associated with and to some degree driven by oxidative stress; oxidants in the brain clearly play a role in the onset of common neurodegenerative disorders such as Parkinson's and Alzheimer's. Oxidative stress is even at the root of the overexuberant lung inflammation which is what really kills people when they get killer flus.

So it's not a question of whether oxidant stress should be controlled to protect us from a wide range of health disorders. Clearly it should. The question is how to do it effectively.

As noted, Offit cites various studies in which antioxidant vitamins have failed to provide benefit, or have even been associated with negative outcomes. There are credible explanations for this. It's crucial to employ the right vitamins, minerals, and phytochemicals if you want to achieve health protection. Vitamin E – alpha tocopherol – has yielded disappointing results for two key reasons. One is that, in people with normal nutrition, vitamin E's antioxidant activity is rather weak and lacking in versatility. It can diminish oxidative damage to cell membranes to a degree, but most of the adverse health impacts of oxidative stress have nothing to do with membrane damage, and baseline vitamin E status in normally nourished people is already adequate to achieve significant protection in this regard. And a likely reason why alpha-tocopherol can actually have a slightly negative impact on health is that it blocks tissue uptake of another form of tocopherol – gamma-tocopherol - that quenches a very dangerous, mutagenic type of free radical known as peroxynitrite. Vitamin E is just one member of a family of compounds found in our food known as tocopherols. Gamma-tocopherol is actually a more prominent constituent of natural diets than is vitamin E – but for arcane reasons only the alpha form has been considered a vitamin and emphasized in clinical studies. Foods naturally rich in alpha-tocopherol typically provide even higher amounts of gamma-tocopherol – which possibly explains why, in people who get all of their vitamin E from natural foods, higher blood levels of vitamin E often correlate with better health outcomes. Smart health advocates have long insisted that clinical studies with vitamin E should employ “mixed tocopherol” preparations that include balanced amounts of alpha- and gamma- and other natural

tocopherols, but their recommendations have so far fallen on deaf ears. The fact that alpha-tocopherol supplementation was associated with a modest but significant increase in risk of prostate cancer in a recent study, may actually constitute indirect evidence that the amounts of gamma-tocopherol provided in ordinary diets help to prevent this cancer – as suggested by animal studies.

In regard to beta-carotene, this also is a rather weak antioxidant. It has been tested for cancer prevention because some studies have found that people with relatively high beta-carotene levels tend to have lower risk for certain cancers. It should have been realized that this might simply have meant that people with diets higher in fruits and vegetables are at lower cancer risk – especially since beta-carotene has not been notably protective in animal models of cancer induction. But nonetheless beta-carotene received considerable hype, and was tested in large-scale clinical trials. By a stroke of very bad luck, it turns out that the oxidants in tobacco smoke can turn beta-carotene into a compound that blocks effective vitamin A activity in the cellular lining of the lungs – actually increasing cancer risk. So studies with beta-carotene in smokers had a negative outcome. We now know that it is a bad idea for smokers to take large doses of beta carotene; it may also be a bad idea for them to ingest large amounts of carrot juice on a regular basis.

Vitamin C supplementation, although it has not proven harmful, has not produced large benefits in most studies because, once a person has a reasonably decent diet with a meaningful level of fruits and vegetables, vitamin C levels in the blood are already sufficiently high, such that raising them higher won't get extra vitamin C into most cells. The real interest in vitamin C these days is in the use of massive intravenous doses in cancer therapy – which can actually kill some cancers selectively by inducing excessive oxidative stress!

Some years ago, supplemental selenium showed a marked cancer preventive effect in a large controlled study. The people who designed this study made sure that they targeted people in an area of the country where selenium soil levels, and hence selenium intakes, are relatively low. Selenium is necessary for the production of several antioxidant enzymes which potentially can reduce cancer induction. But once selenium intakes are sufficiently high, you don't make more of these enzymes when you supplement with selenium. An attempt to replicate the promising first study, focusing on prostate cancer, was unable to replicate the positive findings of the first study – likely because no effort was made to recruit subjects with relatively poor baseline selenium status! The real potential for supplemental selenium as a health promoting agent may be in parts of Europe and Asia where selenium status tends to be relatively poor; Americans who eat selenium-rich mid-Western wheat tend to have adequate selenium levels without supplementation.

Unfortunately, European clinical researchers have been notably derelict in studying the impact of optimal selenium status on health outcomes. But this may be changing – in a recently published 5-year double-blind clinical trial conducted in selenium-poor Sweden, elderly subjects supplemented with the antioxidants selenium and coenzyme Q10 experienced only half the cardiovascular mortality seen in those receiving placebos. Was Dr. Offit simply unaware of this one?

So if alpha-tocopherol, beta-carotene, vitamin C, and selenium have their inherent limitations and, in some instances, real drawbacks, what does one do for effective antioxidant protection? Gamma-tocopherol and mixed tocopherols may have real potential for benefit, but haven't been evaluated in major studies. The carotenoids lutein and zeaxanthin provide important antioxidant protection for the retina,

and may help prevent macular degeneration; many diets are low in these phytochemicals. Astaxanthin, a carotenoid found in certain algae, appears to have much greater efficacy than vitamin E for protecting membranes from oxidative damage.

There are many phytochemicals found in fruits, vegetables and teas – like the polyphenols found in green tea, or the isothiocyanates provided by cruciferous vegetables, that promote oxidant defense by stimulating our cells to make increased levels of antioxidant and carcinogen-detoxifying enzymes, as well as the key intracellular antioxidant glutathione. Not surprisingly, recent Japanese studies are finding that people who drink a lot of green tea have notably superior health outcomes as they get old. And the antioxidant polyphenols in green tea can of course be provide in pill form. The hormone melatonin, likewise available as a supplement, also functions as an antioxidant by boosting cellular expression of antioxidant enzymes and glutathione; diminished melatonin activity appears to play a role in the elevated risk for breast and prostate cancers in people who work night shifts. Cellular glutathione levels can also be boosted with the amino acid derivative N-acetylcysteine – which notably reduced symptoms associated with flu in an Italian clinical study with elderly people that has been almost wholly ignored.

High doses of the vitamin folic acid have shown amazingly potent and protective effects in rodent studies, and some year ago Dr. Kurt Oster reported that this strategy was very beneficial in patients with heart and vascular disease. Despite a couple of small clinical studies that recently have suggested that Oster might have been right, this approach has also been swept under the rug. And perhaps the most promising of antioxidants is a compound in spirulina known as phycocyanobilin. This agent is exciting because it has been shown to mimic the antioxidant impact of its structural analog bilirubin, which functions to inhibit the enzyme complex NADPH oxidase, the chief source of oxidative stress in a wide range of health disorders. This likely explains why, in animal studies, oral spirulina has proven to be protective in an amazingly diverse array of models of human disease. Yet the powers-that-be have so far shown no interest in evaluating spirulina for clinical use.

Just last month, British researchers published an amazing study which evaluated health outcomes in people who have “Gilbert syndrome” – a harmless genetic variant in which blood levels of the potent antioxidant bilirubin are elevated throughout life. When the researchers compared over 4,000 people who had this syndrome with age- and sex-matched controls over about 9 years of follow up, they found that the people with Gilbert syndrome died off at literally *half the rate* as people who didn’t have this syndrome. This strongly suggest that the body’s most potent antioxidant, bilirubin, can confer remarkable health protection over a lifetime. Bear that in mind when someone tries to argue that oxidants aren’t good for you, or that antioxidant measures are inherently counterproductive.

And it should be noted that, in the large studies in which supplementation with high doses of alpha-tocopherol or beta carotene had some adverse health outcomes, there is not a shred of evidence that suppression of oxidative stress had anything to do with these results.

So it’s not really a question of whether controlling excessive oxidative stress is useful – it clearly is. The question is, how can we do this effectively? Clearly, the initial choices of the often none-too-insightful groups that organize mega-expensive clinical trials have been less than optimal. So let’s learn from our failures, and find more effective ways to control the oxidative stress that is at the root of so many of our prominent health problems.

And we also should acknowledge that we don't want to absolutely eliminate the production of oxidants – it's quite true that oxidants play a key role in the ability of our immune systems to neutralize infectious organisms, and that, at low levels, they play a useful signaling role in our body's cells. So the point is not to wholly eliminate the production of oxidants – that would be a bad idea – but rather to prevent excessive production of these oxidants. The good health status of people with Gilbert syndrome likely shows that this can be achieved without notable harm.

Offit regrets the fact that the FDA can't force supplement manufacturers to prove that their supplements are safe before marketing them. But the practical import of such a regulation would be to effectively ban most supplements – supplement makers can't patent most of the compounds they market, they have to compete with modest profit margins, and hence couldn't possibly afford the massive clinical trials that would be required to prove the absolute safety of their products.

Back in the late nineteenth and early twentieth centuries, people had the crazy idea that contraptions could be developed that would enable people to fly. A lot of people died trying to realize this dream. If people like Offit had had their way, the government might have clamped down on these lunatics for their own good – and the aviation industry would never have gotten off the ground. The situation with supplemental nutrition may be analogous. Mistakes are going to be made along the way, and a lot of hopeful expectations are going to be dashed. But if we keep trying, using our best insight and imagination, sooner or later supplemental nutrition – and notably supplemental antioxidant nutrition – is going to make a great contribution to human health that eventually will be documented in credible clinical studies. But we don't need to have our government stand in the way of this progress. Government has a right to call to account supplement companies – or any other companies – that make overtly false representations regarding their products. And government can play a very positive role by sponsoring and funding clinical trials that can provide rational guidance to the public in its choices of supplemental nutrition. But it has no business blocking innovation and preventing people from using the supplements they choose to use out of their own free will. That would surely have a very negative impact on the future of human health.

One final point: the title of Offit's essay is "Don't Take Your Vitamins". Presumably his editor thought that this provocative directive would boost readership. But it's dubious advice. A lot of research now suggests that increased intakes of vitamin D and/or vitamin K2 may be protective with respect to a vast range of disorders – cancer, vascular disease, diabetes, osteoporosis, autoimmunity, and possibly even neurodegenerative diseases. High doses of the B vitamin niacin have long been used as an aid to vascular health - and we've mentioned the potential of high-dose folic acid (another B vitamin) in that regard. Supplemental vitamin B12 is frequently beneficial for vegetarians and the elderly. Flippantly dismissing all vitamin supplementation is likely to be very counterproductive.

For a more ample discussion of the potential of antioxidant supplementation, you can see this monograph by Mark McCarty posted on-line: http://catalyticlongevity.org/prepub_archive/FSAT9.pdf.

Addendum

In an article published in The Atlantic magazine, entitled The Vitamin Myth – Why We Think We Need Supplements, Dr. Offit is back at it again. In this essay, he refers to Dr. Linus Pauling as “arguably the world's greatest quack”.

It is true that, in the latter decades of his very long life, Dr. Pauling went way out on a limb with his predictions regarding the protective powers of vitamin C – a limb that was readily sawed off by subsequent clinical research. But his introduction of the concept “orthomolecular medicine” – medicine which employs compounds present naturally in the body – was a very worthwhile innovation; and I don’t think there is any serious dispute that his advocacy of vitamin C was sincere and well-intentioned, hardly meriting a term of opprobrium such as “quackery”. And Offit fails to mention that Cameron and Pauling’s original publication on vitamin C as a cancer therapy has within recent years given rise to an approach to cancer control that has credibility and shows real promise – intravenous ascorbate therapy.

In his final sentence, Dr. Offit ridicules Pauling for dying of prostate cancer – at age 93!

Aside from his criticism of Dr. Pauling, there is little in Offit’s new essay that hasn’t been dealt with in my commentary above. The exception is his citation of an epidemiological analysis which found that elderly women using multivitamins were at a 2.4% higher risk for death than those not using such supplements. But a possible explanation for this finding is that women with health problems might have been more motivated to use supplements than those that were healthier – this was not a double-blind study. (And the study’s finding linking iron supplement use to increased mortality wasn’t surprising – increased body iron levels may increase cancer risk by promoting oxidative damage to DNA, and most health experts only advise iron supplements for those who are deficient in this mineral. The standard inclusion of iron in the most heavily promoted multivitamin-mineral supplements may help to explain why the results of such supplementation haven’t been more uniformly positive.)

Not surprisingly, Dr. Offit fails to mention a recent study that is much more definitive – in that it was a lengthy double-blind clinical trial. Men who took a Centrum™ iron-free multivitamin-mineral supplement for a number of years were found to be 8% less likely to develop cancer than those receiving a placebo.

Dr. Offit expresses perplexity that supplement sales continue to grow despite various disappointing studies reported in the popular press. But there is a reason why supplements remain popular. People with common sense realize that it is most unlikely that their often catch-as-catch-can daily diets are going to provide them with consistently optimal intakes of all of the vitamins, minerals, ancillary nutrients, and protective phytochemicals. So they seek out supplementation. The fact that the supplements they choose to use aren’t always as protective as we would prefer them to be is not surprising – nutrition is a very complex science, and the science of supplementation has a long way to go to reach maturity. (Not to mention the fact that many purveyors of supplements are businessmen keener on exploiting fads than making a real impact on health.) But rational supplementation – which has already conquered once common disorders such as scurvy, beri beri, and pellagra – will eventually make a much broader contribution to health. Simply dismissing supplementation globally as dangerous fad is as irrational as any of the dubious “alternative” health beliefs which Offit rightly deplors.