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## Mixed Messages

### Antioxidants Fight Disease (Except When They Make It Worse)

By Christopher Wanjek  
 Special to The Washington Post  
 Tuesday, August 7, 2001; Page HE01

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It used to be so simple, a battle between good and evil.

Rogue chemicals called free radicals roam about the body like brazen street punks, the story went, smashing cellular walls and roughing up innocent DNA molecules, causing cancers and the diseases of middle and old age.

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Their flagrant disregard for the law would continue unchecked if it weren't for swashbuckling antioxidants swooping in on the wings of dietary supplements, disarming the free radicals of their menacing electrons and converting them into respectable molecular citizens.

At least that's how the theory went. And the public bought it – both the story and millions of doses of antioxidant supplements, which they believed would reduce disease, boost system performance and maybe even slow the aging clock. But as a bewildering cascade of contradictory, inconclusive and outright negative research reports over the past several years suggests, the human body isn't governed by a B-movie script. The antioxidant story isn't as simple as some – largely, those who make and sell them – would have us believe.

"Free radicals are as good as they are bad," says Walter Bortz of Stanford University Medical School. He is a past president of the American Geriatric Society and author of several popular books on aging and scientific articles on vitamins. He says that antioxidants in high doses may do the body harm; in other cases they may help. We simply don't know yet which ones do which and when.

"It's a very complicated story," he says.

You know many antioxidants by name, whether you take them or not: vitamins C and E, beta carotene and selenium are just the most common. Their purported health benefits adorn the packaging for everything from

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cereals to cosmetics. One can easily walk through the aisles of any grocery, drug or vitamin store thinking that antioxidants are scientifically validated wonder pills. They're not, "although the data don't seem to make any difference to the sales of supplements," says Richard Veech, chief of the Laboratory of Membrane Biochemistry at the National Institute on Alcohol Abuse and Alcoholism, who has reported on the interplay of free radicals and antioxidants for more than 30 years.

Americans spent \$31 billion on vitamin supplements in 1999, according to the U.S. General Accounting Office. Nearly \$2 billion of that was for vitamins E and C, beta carotene and selenium, according to Nutrition Business Journal. Up to 30 percent of the population is taking antioxidant supplements regularly, according to the American Heart Association.

While the efficacy of antioxidant supplements remains gospel in the health-marketing community, Bortz says the accumulating scientific record does not verify it. For every study that shows benefits, he says, there is another study that doesn't.

So with antioxidants and free radicals now seen as playing dual roles of good guys and bad guys, just what exactly is the state of antioxidant research? And what health claims can you believe? The experts – you were about to guess this – have a variety of opinions.

### **Armor All for the Body**

It's generally recognized that antioxidants have the ability to serve as sort of a rust protector for the body, putting a stop to a process called oxidation.

Important molecules in the body, such as those that form the walls of arteries, become oxidized when they lose an electron. Once oxidized, they become unstable and easily break apart.

The culprit, without a doubt, is the free radical, Veech says. Free radicals are highly reactive molecules, or single atoms with unpaired electrons, looking for a mate. So they steal an electron from the first thing they encounter, perhaps a cell wall or a strand of DNA. As free-radical damage mounts, cells can no longer perform properly. Tissues degrade. Disease sets in. An excess of free radicals has been cited in the development of cardiovascular disease, Alzheimer's disease, Parkinson's disease and cancer. Aging itself has been defined as a gradual accumulation of free radical damage.

Yet not all free radicals are bad. In fact, free radicals are necessary for life, according to Britton Chance, professor emeritus of biophysics, physical chemistry and radiologic physics at the University of Pennsylvania, a renowned expert on free-radical production. The body cannot turn air and food into chemical energy without a chain reaction of free radicals, for instance. Free radicals are also a crucial part of the immune system, floating through the veins and attacking foreign invaders. They help fight against bacteria.

Without free radicals, says Chance, "we couldn't have this conversation."

Free radicals are a natural byproduct of breathing; antioxidants mop some of them up. A balancing act emerges, says Veech. The body hopes to avoid

excessive free-radical production, but it certainly doesn't want to get rid of all of them.

A diet rich in fruit, vegetables, nuts and some meats supplies most people with the antioxidants needed to walk this tightrope, according to a report last year from the Institute of Medicine. The IOM could find no convincing evidence that the bulk of the American population needs additional armaments in the form of antioxidant supplements to fight free-radical damage. The very notion that free radicals, produced naturally, are some type of unwelcome houseguest is silly, according to Veech.

Veech says that free radicals have been incorporated into the functioning human system over millions of years of evolution. The idea that they should be wiped out or minimized is nonsense, he says.

"God," he says, "is no fool."

### **Low Levels, High Levels**

Studies indicate fairly consistently that having too few antioxidants is a bad thing. One study, published in 1983 in the British medical journal *The Lancet*, found that people with low blood levels of selenium were twice as likely to develop cancer compared with people with normal levels. Another study, published in 1986 in the *New England Journal of Medicine (NEJM)*, found that patients with a certain type of lung cancer were four times more likely to be deficient in beta carotene than a control group.

A 1989 study from the Netherlands associated low selenium levels with an increased risk of heart attacks. More convincingly, the Harvard-based Physicians Health Study – which has recorded the lifestyles of some 50,000 male health professionals for the past 15 years – found that men who ate a diet rich in vitamin E (from nuts, seeds and soybeans) were half as likely to develop heart disease as those with very low levels of dietary vitamin E.

Although these epidemiological studies suggest an association between antioxidants and good health, this does not mean that the antioxidants caused the improved health. Nor does it imply that taking antioxidants in a pill form improves health. In the studies cited above, it is not clear what is responsible for the lower levels of the nutrients – a poor diet, a certain environment, some unknown metabolic factor.

Taking generous doses of antioxidant supplements showed some promise in studies published in the mid-1990s. Skin cancer patients given daily selenium supplements were twice as likely to survive their cancer as those patients not given selenium, the *Journal of the American Medical Association (JAMA)* reported in 1996. This was a multi-center, double-blind, randomized, placebo-controlled study with more than 1,300 patients – all the markings of good science. The findings were so dramatic, wrote the authors, that they stopped the study after six years so that all patients could benefit from the selenium supplement.

Other studies showed similar positive results: Vitamin E postponed the onset of debilitating Alzheimer's symptoms in a small study published in the *NEJM* in 1997; slowed the progress of coronary artery disease in a study at the University of Southern California School of Medicine that was published in

JAMA in 1995; cut the risk of cataracts by half in a 1998 Stony Brook (N.Y.) Medical Center study published in the journal *Ophthalmology*; and lowered the risk of prostate cancer in a 1994 *NEJM* article. Vitamin C helped stave off blindness, kidney failure and the need for amputation among diabetics, according to a 1998 Duke University Medical Center report. Extra selenium, a mineral needed only in trace quantities, reduced the risk of prostate, colorectal and lung cancer, according to the National Institutes of Health's Clinical Center (as reported in 1997 and 1998 in journals such as the *American Journal of Epidemiology*, *Cancer Prevention and Nutrition Review*).

Consumers tuned in to these results. Sales of vitamin E grew from \$590 million to \$860 million from 1995 to 1999, according to *Nutrition Business Journal*. Sales of other antioxidants climbed by millions of dollars as well.

But the story doesn't end there. Side by side, over the years, came a wave of neutral and even negative reports about the benefits of antioxidant supplements. One study, reported in *NEJM* in 1994, found that Finnish male smokers were 18 percent more likely to develop lung cancer after taking a beta carotene supplement. In 1997, *The Lancet* published a study of nearly 2,000 men receiving vitamin E, beta carotene, both or a placebo after suffering their first heart attack. The two beta carotene groups were about twice as likely to die from a second heart attack or heart disease as the placebo group, and the vitamin E-only group was about 1.5 times as likely to die.

Other studies showed similar negative results: no evidence that vitamins C and E or beta carotene prevented colorectal cancer; no evidence that these "big three" prevented arteries from re-clogging after angioplasty; no evidence that beta carotene prevented cancer or heart disease in more than 22,000 physicians over 12 years; no evidence that extra selenium prevented cancer in 60,000 nurses; and more bad news for smokers taking beta carotene, this time with a 28 percent higher incidence of lung cancer. These studies were reported in *NEJM* from 1994 to 1997.

Criticisms naturally flowed back and forth, with the pro-supplement camp finding methodological errors in studies casting doubt on pills, and the anti-supplement folks finding similar problems in the work that seemed to contradict their findings. .

Strangely, Veech says, all these studies might be absolutely right, pointing to the complex heart of the matter – that we don't understand the intricate relationship between certain types of antioxidants and certain types of free radicals at different moments over the course of one's lifetime.

"You can't talk about antioxidants en masse," says Veech. "They all have different potentials."

### **The Antioxidant Paradox**

Barry Halliwell of the National University in Singapore wrote a short article in *The Lancet* last year entitled "The Antioxidant Paradox." Halliwell was lamenting the fact that although diets rich in antioxidants seem to have a positive effect on health, popping antioxidant supplements can be either beneficial or harmful, and the results are not at all predictable.

If the chemistry is all the same (that is, pairing up free electrons and converting free radicals to neutral molecules), why would a given antioxidant have different effects at different times on different regions of the body? Several entirely different mechanisms might be taking place, researchers say:

Extra amounts of antioxidants might be turning into pro-oxidants (which promote the removal of electrons from atoms), fueling free-radical production and its damage.

Supplements might do nothing at all because they can't get to where they are needed.

Or antioxidants might not be the magic beneficial chemical in the food we eat after all.

Can antioxidants turn on you? Several studies have shown that people who did not get the daily recommended allowance of vitamin C had an increase in free-radical damage to their DNA. But, paradoxically, people who took megadoses of C also had an increase in DNA damage. The second scenario might happen, Halliwell says, because vitamin C can worsen cell damage once it has already started.

Within a cell, certain metal compounds are released as a result of free-radical damage. These metals themselves can act as a catalyst for further free-radical damage when they are in a "reduced" state, with a missing oxygen or extra hydrogen atom. Antioxidants place metals in this reduced state. Thus, in this environment, antioxidants become pro-oxidants, Halliwell says.

This was demonstrated in laboratory animals exposed to the pesticide paraquat, a known carcinogen. Animals that received vitamin C before exposure were largely protected from cancer. Animals that received vitamin C after exposure didn't fare so well: The antioxidant aggravated the damage caused by the herbicide and led to more cancers.

The American Cancer Society (ACS) advises cancer patients not to prescribe themselves antioxidants because of this potential effect, although it has never been demonstrated convincingly in human studies.

"Think of antioxidants as drugs," says Michael Thun, who heads epidemiological research for the ACS in Atlanta. There are gaps in our understanding, Thun says, and "antioxidants are not necessarily safe or beneficial."

Compounding this is the fact that free radicals can kill cancer cells; that's how some cancer treatment works. And rapidly multiplying cancer cells can use antioxidants to their advantage to fuel their growth, Thun says. So taking antioxidants at the wrong time essentially arms the bad guy with the weapons to stay alive and multiply.

We should point out that none of this has convinced some practitioners of alternative medicine not to prescribe antioxidants for cancer. Many do, and insist mainstream medicine is depriving patients of valuable cures and treatments.

Another baffling complication is that – despite the assurances of pill makers

who advise simply taking their pills by mouth and feeling confident that the body will know what to do with them – no one knows how to get antioxidants to travel where they are needed, when they are needed.

Most free-radical damage occurs in the mitochondria, according to the University of Pennsylvania's Chance. The process of making energy in the mitochondria, called the respiratory chain, depends on the availability of free radicals. And extra free radicals are made in the process.

The mitochondria house a tiny, circular strain of DNA that contains 30 genes. This is separate from the double-helix DNA in the cell's nucleus. The mitochondrial DNA, called mDNA, is often the free radical's first point of attack. When mDNA is damaged, it cannot do its job of creating the proteins (molecular messengers) needed for daily bodily maintenance.

This is where a magic bullet could come in handy, Chance says – something that could penetrate the mitochondria and mop up a rogue free radical set on doing damage, while steering clear of the intricate respiratory chain. Yet mitochondria are veritable fortresses with tough outer walls, moat-like inner barriers and meandering inner walls protecting their precious contents. Proteins get out, but antioxidants have a tough time getting in.

"This is where the problem is," Harmon says, "getting into the mitochondria."

No one is sure whether brute force – which is to say, a megadose of antioxidants – is the way into the mitochondria, says Bortz, who was a colleague of Linus Pauling, the Nobel laureate who recommended megadoses of vitamin C to ward off colds, flus and even cancer. Perhaps the body has more subtle ways of permitting entry.

### **Diet Vs. Supplements**

And so it is that doctors are split on whether to recommend antioxidant supplements to their patients. The camps are broken down into those who believe there are not enough data to make blanket recommendations; those who feel that Americans (particularly children) have such a poor diet that they need a supplement to ensure adequate levels for basic function; and those who say that anyone can benefit from increased antioxidants regardless of how healthy the diet is. A smaller camp sees in the reports about negative effects of antioxidant pills reason enough not to take any.

For Bortz, who is in his sixties and runs a marathon once a year, whether or not to take an antioxidant supplement is "an intellectual issue."

"Anything that will work, I'm for," Bortz says. "I just don't want people spending their money on false hopes. . . . Exercise is the master therapy."

Bortz says "maybe" to vitamin E; "nah" to vitamin C; and "no way" to beta carotene.

Halliwell argues that a varied diet seems to be more healthy than simple supplement-taking because the isolated antioxidant might not be the superhero. Fruit and vegetables are rich in antioxidants, but these plants contain hundreds of other chemicals. Any single chemical or combination of chemicals might pack the therapeutic punch.

Nutrients from food enable the body to make its own antioxidants. Veech says that a chemical produced by the body called glutathione is ultimately responsible for neutralizing free radicals, and the glutathione concentration in cells dwarfs that of the free-radical scavengers such as vitamin C and E. So diet and energy demands determine the amount of free radical generation and removal, with supplements playing a minuscule role, if any.

"The production of free radicals, absent genetic defects, results from normal metabolic processes," says Veech. "Likewise, the destruction of free radicals in a non-harmful manner is also the result of normal metabolic processes.

"People don't want to exercise. They don't want to eat healthy food. They don't want to stop drinking; they don't want to stop smoking; they don't want to stop having dangerous sex. They want to take a pill. Well, good luck."

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## The Funny Thing About Vitamin E

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Even many conservative researchers remain excited about the potential benefits of vitamin E, which is found naturally in vegetable oils (particularly wheat-germ oil), sweet potatoes, avocados, nuts, sunflower seeds and soybeans. The daily recommended allowance is 30 IU, and some, like Thomas Perls, an assistant professor of medicine at Harvard Medical School, recommend up to 10 times that amount. Even a minimum level of vitamin E, Perls said, is hard to get through diet alone.

One theory championing vitamin E is that the oxidation of LDL, the bad cholesterol, is the first step in plaque formation in the arteries. Vitamin E may inhibit this, thus reducing the risk of atherosclerosis and heart attacks. But which study can you trust?

The perhaps aptly named CHAOS (Cambridge Heart Antioxidant Study) found that high doses of vitamin E lowered the risk of a second heart attack — but raised the risk of dying from that second heart attack if it came. The big Italian GISSI-Prevenzione study and the American HOPE study found no effect from vitamin E in preventing heart disease.

Taken as a supplement, vitamin E may also cause bleeding problems, particularly in people taking anti-clotting medications. As a result, the American Heart Association (AHA) does not recommend taking vitamin E supplements.

Annette Dickinson, a vice president at the Council for Responsible Nutrition (CRN), a group representing dietary supplement makers and marketers, agrees that human studies have not shown reasons for taking a vitamin E supplement, but she says this could be for a variety of reasons, including the fact that the studies lasted only a few years, not a lifetime. Supplements may not be an effective quick fix but could yet be found to offer long-term benefits. The data from animal studies on vitamin E's long-term health benefit are "very convincing," Dickinson says.

And while the AHA shies away from advocating vitamin E, many heart doctors are not reluctant to do so. (The amount of vitamin E most commonly used or recommended is 400 International Units.) CRN reports that three-fourths of more than 300 cardiologists it recently surveyed take vitamin E supplements themselves and also recommend vitamin E supplements to their

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patients. These cardiologists were twice as likely as the general population to take vitamin E.

If you do take vitamin E or any antioxidant supplement, you may be in good company. You are not necessarily foolish. It's just that no large health group can advocate antioxidant supplements without more convincing data.

"You either stick to evidence-based medication, or you don't," says Daniel Steinberg, professor of medicine and endocrinology at University of California, San Diego. Steinberg, a member of the National Academy of Sciences, worked on last year's Institute of Medicine report, which found no convincing evidence for the widespread use of antioxidant supplements. "We do not have clear, positive clinical results. At best, the data are mixed."

*Note: Results are expected later this week on a significant study on antioxidants and the treatment of heart disease.*

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## The ABCs of Antioxidants

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### Vitamin A/Beta Carotene

**FUNCTION** Essential for bone development, vision, reproduction and healthy skin; the body converts the nutrient beta carotene into vitamin A.

**FOOD SOURCES** Liver, dairy products, eggs and fish liver oil (vitamin A); dark red, green and yellow vegetables (beta carotene).

**PROBLEMS** Deficiency may lead to skin and eye problems; toxic and life-threatening in high doses.

### RESEARCH FINDINGS

[+]: Lung cancer patients four times more likely than a comparable group without lung cancer to be deficient in beta carotene (NEJM, 1986).

[-]: Male smokers 18 percent more likely than other male smokers to develop lung cancer after taking beta carotene supplements (NEJM, 1994).

[-]: Smokers taking beta carotene supplements had 28 percent higher incidence of lung cancer than other smokers (NEJM, 1996).

[-]: No evidence that beta carotene supplements prevented cancer or heart disease in more than 22,000 physicians over 12 years (NEJM, 1996).

[-]: Significantly more deaths from heart disease in a group taking beta-carotene supplements after first heart attack than in a similar group that did not take these supplements (Lancet, 1997).

### Vitamin C

**FUNCTION** Essential for collagen production for bone, cartilage, tendons and ligaments; may boost immune system.

**FOOD SOURCES** Many fruits, bell peppers, broccoli, sweet potatoes, many leafy vegetables.

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**PROBLEMS** Deficiency leads to scurvy and sluggishness; aspirin interferes with vitamin C uptake; very high doses may cause intestinal problems and kidney stones.

#### RESEARCH FINDINGS

[+]: Helped stave off blindness, kidney failure and the need for amputation among diabetics taking supplements (Duke Medical Center, 1998).

[+]: Four-year study of 19,000 men and women revealed that those with higher levels of vitamin C in the blood, gained largely through diet, had a 20 percent lower chance of dying from cancer and heart disease than those in a group with lower levels (Lancet, 2001).

[+/-]: Protected animals against cancer if given before pesticide exposure, yet promoted cancer if supplement given after exposure (Free Rad Research, 1998).

[-]: Supplements no help in preventing colorectal cancer (NEJM, 1994).

[-]: High doses of vitamin C supplements no help to group of 400 patients with advanced cancer (NEJM, 1979).

[?]: National Eye Institute is wrapping up a seven-year study on vitamin C supplements on cataracts and other eye diseases; results expected later this year.

#### Vitamin E

**FUNCTION** Prevents cell membrane damage.

**FOOD SOURCES** Wheat-germ oil, soybeans, nuts, seeds, sweet potatoes.

**PROBLEMS** High doses may cause bleeding, nausea and diarrhea.

#### RESEARCH FINDINGS

[+]: Supplement lowered deaths from heart disease in two studies (NEJM, 1993).

[+]: Supplement lowered risk of prostate cancer (NEJM, 1994).

[+]: Supplement slowed progress of coronary artery disease (JAMA, 1995).

[+]: Supplement postponed onset of debilitating Alzheimer's symptoms (NEJM, 1997).

[+]: Supplement cut risk of cataracts in half (Ophthalmology, 1998).

[+/-]: Supplement lowered risk of second heart attack but raised risk of dying from that heart attack (Lancet, 1996).

[+/-]: Prevented heart disease in those with diets rich in foods containing E; no effect on reducing stroke (Physicians Health Study, 1996).

[-]: Supplement no benefit in preventing lung cancer; led to higher frequency of stroke (NEJM, 1994).

[-]: Supplement no effect in preventing heart disease in GISSI-Prevenzione Italian study (Lancet, 1999) and HOPE American study

[?]: NIH is funding several large randomized, double-blinded clinical trials investigating vitamin E supplements and heart disease; first results expected in 2002.

## Selenium

**FUNCTION** A mineral essential for normal functioning of the immune system and thyroid gland.

**FOOD SOURCES** Vegetables and grains grown in areas whose soil contains selenium, such as the American Midwest.

**PROBLEMS** Deficiency may lead to thyroid and heart problems; excess can lead to selenosis, which causes intestinal problems, nerve damage, hair loss, white blotchy nails. (Narrow window for adequate intake: don't exceed 400 micrograms per day.)

## RESEARCH FINDINGS

[+]: People with low selenium levels from diet were twice as likely as those with normal levels to develop cancer (Lancet, 1983).

[+]: Skin cancer patients given selenium supplements were twice as likely to survive as those who did not take the supplements (JAMA, 1996).

[+]: Reduced risk of prostate, colorectal and lung cancer was associated with dietary intake (NIH Clinical Center, 1997-98).

[-]: No added cancer protection from diet rich in selenium (60,000-person Nurses' Health Study).

[?]: NIH is funding several large randomized, double-blinded clinical trials investigating selenium supplements and cancer; first results expected in 2002.

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