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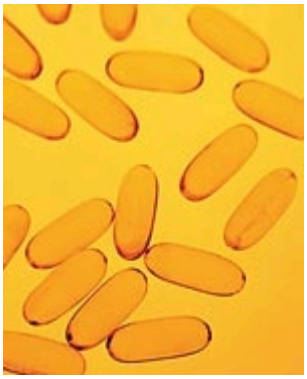
REPORT

Antioxidants

By Terri Mitchell



It's hard to imagine a health world without antioxidants. They stand alongside aspirin and Band-Aids as mainstays of the American landscape. Hundreds line the shelves of Wal-Mart and Rite Aid, avidly sought by the masses. Yet 25 years ago, antioxidants didn't exist for most people.

It was a strange turn of events that made antioxidants mainstream. In a brew that threw together a physicist, an oil chemist, an adventurer, and a Hollywood talk show host, what emerged was the idea that average people could use science to advance their health, and the antioxidant boom was born.

Oh, and Playboy. In 1968, MIT wunderkind Durk Pearson read an article from the magazine about Dr. Denham Harman's theory on free radicals and aging. Intrigued, Pearson and Sandy Shaw dug into the UCLA library and pulled out Harman's scientific publications. Harman, a chemist working in the then-obscure field of oxygen chemistry for the research arm of Shell Oil, had come up with the notion that the by-products of oxygen reactions ("free radicals") cause aging. (Anything that aged rubber probably wouldn't do much for internal organs, Harman rightfully reasoned.) Armed with degrees in physics and chemistry, Pearson and Shaw immediately took to Harman's scientifically based concept, and began looking into it further. That was fine, and it might have been the end of it except for the well-timed entrance of a genuine Indiana Jones-type adventurer named Jack Wheeler.

Wheeler was a regular guest on the then-popular Merv Griffin talk show, and when he went to California for filming, he hung out with Durk and Sandy. They had become immersed in the idea of testing Harman's theory, and every time Wheeler showed up, they regaled him with their latest ideas about aging and free radicals. Durk's knack for whacking complicated science down to size got Wheeler to thinking there might be a wider audience for the finer points of free radical chemistry (hey, the stuff was interesting the way Durk explained it). So Wheeler approached Merv about Durk going on the show. Incredibly (it seems now), Merv consented, and the rest is history. Durk's second visit provoked over 100,000 letters—the single most popular appearance ever recorded for a talk show. As Wheeler tells it, Merv's entire office was covered in letters asking Durk and Sandy questions about health and aging.

Clearly, the idea that average people could use science for their own benefit was immensely popular. Until then, science on free radicals wasn't even known to most chemists, let alone medical doctors. TV viewers of the time had two health care options: they could go to a doctor who would give them a drug, or consult a nutritionist who would make them eat wheat germ and desiccated liver. Here was something different. Here was a guy in lederhosen talking about a whole new world of antioxidants: vitamins and drugs, amino acids and hormones—things that a person could get ahold of and actually try. This was beyond prednisone and liver tablets. Now people could actually do something about their widening girth, chronic allergies, and cross-linked skin. And aging of all things! Durk said you could actually do something about aging! The fact that the man looked like an escapee from a commune was of no importance. Free radicals—boo! Antioxidants—yea! Americans had new weapons against the things that plagued them.

That was then and this is now. Things are a little more complicated than they seemed to be back in the Merv era. The connection between oxidative damage and the degenerative diseases of aging, as well as aging itself, remains strong. Yet the world of antioxidants has gotten substantially more complex.

THE VITAMIN E SHIELD

Vitamin E is one of America's most popular antioxidant supplements. According to a recent USDA study, that's a good thing, because only 2.4% of American women and 8% of men get enough of the vitamin from food.[1]

Vitamin E is fat-soluble and reduces the level of free radicals associated with lipids, such as those that affect cholesterol and those that affect the brain. For this reason, vitamin E has been intensively studied for its ability to prevent cardiovascular and Alzheimer's diseases.

Taking relatively high doses of vitamin E (2000 IU/day) may protect against Alzheimer's disease, especially if begun early in life and combined with relatively high doses of vitamin C (1000 mg.)[2-4] There are two good reasons for people worried about Alzheimer's to take vitamin E: Alzheimer's patients have significantly reduced levels of antioxidants in their brains and blood, which can be raised with supplements such as vitamin E; and biochemical studies show that the high level of oxidative stress found in Alzheimer's patients is ameliorated with antioxidants, including vitamin E.5-9 Vitamin E is one of the bestknown antioxidants, but by no means the only one.

FREE RADICALS AND INFLAMMATION

One of the most important medical discoveries of the past decade is the connection between inflammation and diseases like cancer and Alzheimer's. The finding that people who take anti-inflammatory drugs have a lower risk of cancer was, at first, very surprising. How could something that lowers pain and reduces swelling possibly inhibit cancer? Researchers soon discovered inflammatory factors that enhance the ability of cancer cells to multiply and spread. Now we know that things that block inflammation—including aspirin—also impede cancer.

Things have been ratcheted up in the antioxidant world with new research showing that some antioxidants have powerful anti- inflammatory action. Although inflammation involves free radicals, it's somewhat more complicated, involving the activation and inactivation of genes as well. Some antioxidants also block inflammation in addition to having radical-scavenging effects.

For example, when the antioxidant curcumin is given as a dietary supplement to animals with a mouse model of Alzheimer's disease, it blocks the oxidation of certain proteins. This is the antioxidant effect, which in turn lowers the activation of inflammation signals. The net result is that abnormal Alzheimer's proteins are lowered by about 40%.[10] This may slow disease progression. If this experiment held up in humans, and abnormal proteins could be retarded by 40%, it might translate into years of life that would otherwise be lost to a disease for which there is presently no cure.[10]

Combinations of antioxidants can have greater effects than single agents on certain types of inflammation. A recent study focuses on an inflammation marker known as C-reactive protein (CRP), which is elevated in people who may appear healthy but could have a sudden heart attack and die. This study is important because it used baboons, whose biochemistry is more human-like than that of rodents.[11] It shows that elevated CRP can be dramatically reversed with a combination of two antioxidants. Vitamin E (DL-alpha-tocopheryl acetate) at a human dose of approximately 200 IU/day reduces CRP by 50%. Adding coenzyme Q10 further reduces CRP by about 20% more, for a 70% reduction overall.[11] Two other studies of primates demonstrated beneficial effects of vitamin E, for both the prevention and treatment of cardiovascular disease.[12,13]

Curcumin and vitamin E are only two of the many antioxidants that inhibit inflammation. Information on others can be found in past and future issues of this magazine. The important thing is to be aware that some antioxidants go a step further and reduce inflammation, which may block serious diseases including cancer.

DOES DIET INCREASE FREE RADICALS?

When free radicals first hit the radar screen, the emphasis was on taking antioxidants to counteract them. While this is still a good idea, the complementary approach is to generate as few free radicals as possible in the first place. Diet, it has been discovered, can undermine this goal.

Iron and copper are required elements of human nutrition. However, an overabundance of either or both promotes free radicals that destroy healthy tissue. Iron has been the focus of several recent studies that are extremely important.

One of them shows that the risk of type II diabetes increases with greater amounts of iron in the diet. In a 12-year study of more than 30,000 men, "heme" iron from red meat doubled the risk of type II diabetes.[14] Dietary heme from red meat is also a potent promoter of colon cancer.15 And an analysis of two large American studies shows that excess iron increases the risk of a fatal heart attack more than fivefold and raises the risk of all-cause mortality over threefold.[16] Iron from plant sources is known as "nonheme" iron and doesn't appear to carry the same risks. One reason may be that it's not absorbed as well. Plants contain natural metal inhibitors.

The principal source of iron in the American diet is fortified cereals such as Kellogg's Product 19, which contains 18 mg in a one-cup serving. The iron in fortified cereal, however, is non-heme iron, and its absorption is impeded by the phytate in the cereal. By comparison, three ounces of beef contain 3 mg of heme iron that

is readily absorbed.[17] The US Food and Nutrition Board has set an upper limit on iron intake of 45 mg/day. Postmenopausal women and men are advised to avoid highly fortified foods and iron supplements.[18]

Copper is another metal that promotes damaging free radicals. Copper combined with homocysteine (a natural byproduct of methionine metabolism) creates a lethal brew that can harm the brain and heart.[19,20] Copper promotes the spread of cancer, and a copper chelator known as tetrathiomolybdate has been successfully used to combat some types of cancer, including squamous cell.[21,22]

Copper accumulates in the brains of Alzheimer's patients.[23] The phytocompound curcumin again appears on the scene. It has been proposed that curcumin be used as a treatment to chelate copper and prevent it from triggering free radical damage.[24] Curcumin naturally chelates both iron and copper.[24] Resveratrol, from wine and grapes, is also a copper chelator that keeps the metal from oxidizing LDL (low-density lipoprotein),[25] which can be found in the brain as well as the heart and blood vessels.

Although resveratrol doesn't chelate iron, it's one of the strongest antioxidants ever discovered for protecting against iron-induced free radicals.[26] Quercetin, a natural cousin of resveratrol in grapevine and other plants, neutralizes both iron and copper better than 10 other phytocompounds.[27] "Remarkable protection against lipid peroxidation" is how researchers in Italy described quercetin after studying its ability to chelate iron in LDL.[28] This is important, because current research indicates that it's not cholesterol per se that's bad, it's oxidized cholesterol—that is, oxidized LDL.

The number-one source of copper in the American diet is beef. According to the USDA database, beef contains whopping amounts of copper. Three ounces of American beef contain nearly 4 mg of copper. By comparison, one cup of chickpeas contains 0.58 mg.[29]

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ANTIOXIDANTS REDUCE MORTALITY

Researchers in Belgium theorized that people have a certain balance of antioxidants and free radicals in their bodies, and if the balance were tipped toward free radicals, they would be more likely to die. So they came up with a scoreboard for oxidative balance in a group of smokers.[30] Using diet as the basis, the smokers were divided into groups with low, medium, and high oxidative stress (which generates free radicals). Those with the highest iron intake and/or the lowest antioxidant vitamin intake had the worst score. At follow-up 10 years later, those with the worst score (based on high iron intake plus low beta-carotene and vitamin C intake) had a 44% higher risk of all-cause mortality and a 62% higher risk of cancer mortality than those with a good level of antioxidants.[30]

The study is confirmed by others showing that blood levels of antioxidants are “strongly predictive of mortality.”[31] Lycopene and other carotenoids can slash the risk of mortality in half in nonsmokers.[32] Antioxidant supplements and vitamin E can likewise reduce the risk of breast cancer recurrence,[33] and lycopene can do the same in relation to oral cancers.[34] Adequate levels of vitamin E, vitamin A, and lycopene are associated with a reduced risk of microangiopathy-related cerebral damage,[35] and vitamins C and E taken as supplements at levels much higher than the US RDA can help protect against ovarian cancer.[36] These findings are from just a few of the hundreds of published studies.

DIFFERENT RADICALS, DIFFERENT ANTIOXIDANTS

Of the several different types of free radicals, some are related to fat and others to water. Antioxidants that are great at scavenging one type of radical may have no effect on another. This was illustrated by researchers at the USDA’s Fruit Laboratory who studied different berries.[37]

The researchers found, for example, that juice from the “Hull Thornless” blackberry could inhibit four different types of radicals (hydroxyl, superoxide, singlet oxygen, and hydrogen peroxide) a lot better than vitamins E and C and all other berries tested. They discovered that beta-carotene is good at stopping singlet oxygen, but has no effect against hydrogen peroxide. Alpha tocopherol inhibited singlet oxygen radicals by 22.5%, better than strawberries at 15.41%.[37]

Not only does the type of berry make a difference, but whether it’s organic also counts. Researchers at the University of California at Davis found that organic frozen corn contains 50% more vitamin C than regular frozen corn, and that levels of phenolics were likewise higher in organic frozen strawberries.[38]

THE BODY’S OWN ANTIOXIDANTS

It’s not possible to avoid free radicals. Humans are bombarded with radical-generating radiation and toxins every day. On top of that, the body makes its own radicals. Energy production creates them and so does the immune system, where radical promoters such as hydrogen peroxide are synthesized inside cells and used to destroy invaders such as bacteria.

The body, however, has a remedy for its radicals: it creates its own antioxidants. Some of them are in the form of enzymes, which rely on metals such as selenium and zinc; these include glutathione peroxidase, superoxide dismutase, and catalase. Others are sulfur-related, and in-clude lipoic acid, N-acetylcysteine, and glutathione.

Cysteine, one of the sulfur-related antioxidants, is a critical component of glutathione, a major antioxidant for the liver, kidney, blood cells, and lungs, which are said to have an since they are exposed to both external and internal radicals.[39] Prolonged or very intense oxidative stress can deplete glutathione and leave cells vulnerable to free radical damage. A quick route to glutathione depletion is drug and alcohol abuse.

Lipoic acid is another sulfur-related antioxidant synthesized in the body. It is unique because it can scavenge both water- and fat-type radicals, unlike most other antioxidants that go after one or the other. In a study of humans taking 600 mg of lipoic acid a day, three major areas of oxidative stress—LDL peroxidation, protein carbonyls, and isoprostanes—were reduced, a clear demonstration of lipoic acid's multi-system activity.[40] Lipoic acid is well known for its beneficial effects against diabetes, and has been used extensively in Germany and other countries to help manage diabetic neuropathy, protect the eyes, and more.[41-43] Not only does lipoic acid help reverse the effects of diabetes, but Korean researchers recently demonstrated that the supplement can also help prevent diabetes from developing in the first place, at least in overweight rats.[44]

Glutathione levels decrease with age.[45] Part of the problem occurs at the genetic level, where the genes that help manufacture it slow down.[46] Supplemental lipoic acid not only can help reverse this loss and protect the heart and brain, but also can actually jump-start an aging gene into working again.[45-47]

Supplemental lipoic acid and L-carnitine are a powerful antidote to age-related antioxidant and energy loss. The two work synergistically in the body's power plants known as mitochondria.[48]

ANTIOXIDANTS AND CHEMOTHERAPY

A study from the MD Anderson Cancer Center found that 62% of the patients at its clinics were taking herbs and/or vitamins,[49] yet oncologists know little or nothing about how these supplements might affect conventional cancer treatment.

Chemotherapeutic drugs and radiation generate free radicals that damage both cancerous and healthy cells. It was previously thought that causing free radical damage to cancer cells was the principal way these treatments work. However, new research indicates that that's not necessarily true. Some chemotherapies actually work better when free radicals are reduced.[50] There is no definitive answer at the present time as to whether or not antioxidants should be taken during chemotherapy; it may depend on the type of cancer and type of drug being used.

Very few studies of antioxidants and chemotherapy have been done to date. Some confirm that antioxidants are beneficial during cancer treatment, while others indicate that some antioxidants may interfere with treatment. Still others show that certain antioxidants may enhance the cancer-killing effects of chemotherapeutic drugs.

As an example of the type of research that's emerging, researchers at Columbia University report that children with acute lymphoblastic leukemia whose intakes of vitamin E, carotenoids, beta-carotene, and vitamin A are below the recommended daily allowance have more side effects from chemotherapy.[51] In another study of women undergoing treatment for breast cancer, vitamin E or multivitamins helped maintain white blood cell counts (neutrophils), while folate had a negative impact on white cells.[52]

British researchers analyzed levels of selenium in people diagnosed with B-cell non-Hodgkin's lymphoma.[53] They found that if patients had high levels of selenium upon entering treatment, they had a better response, could tolerate higher doses, and were more likely to have long-term survival.

Italian researchers gave 300 mg of vitamin E a day to people undergoing chemotherapy with the drug cisplatin. When the vitamin was given prior to the drug and for three months after, toxicity to the brain was reduced from 85% to 30%. It's not known whether a higher dose or different form of vitamin E might have slashed toxicity even further.[54]

Melatonin is well documented as a powerful antioxidant, particularly against radicals caused by radiation.[55] In a study of people with metastatic non-small cell lung cancer, 20 mg of melatonin taken each night increased their ability to tolerate chemotherapy and achieve a better result. Three of 49 people were still alive at five years in the melatonin group, whereas none of the people in the group not receiving melatonin was still alive at two years.[56]

These and other studies are showing the effects of antioxidants in humans treated for cancer. Many animal studies already show beneficial effects for certain antioxidants used in conjunction with certain chemotherapies. But caution is warranted because some antioxidants can interfere with the ability of some chemotherapies to kill cancer cells.[57]

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CONCLUSION

In the relatively short time that antioxidants have been on the radar screen, much progress has been made in understanding just how important they are for health and longevity. The critical roles they play in counteracting the toxic effects of environment and normal cellular processes are undisputed. Block a critical antioxidant in a laboratory fly, and it will live less than a quarter of its life span. Add more of the same antioxidant, and it will live much longer that it's supposed to.[58] People with greater amounts of antioxidants in their blood are more likely to survive cancer and critical illness.[59-61]

Strange coincidences and blind luck put free radical research on the map—a field that may have been destined to a dusty corner until the day in 1954 when Dr. Denham Harman had the epiphany that the same chemical reactions that age windshield wipers might age human beings. This epiphany was made possible by his training in both fields—petroleum chemistry and medicine, that is. Free radical research might still be languishing in obscure journals had not Durk Pearson and Sandy Shaw realized the potential of Harman's "free radical theory of aging" to be useful to humans in everyday life. Such is science.

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