The connection between antioxidants and health constitutes one of the most successful conjectures in modern science. Theories linking oxidative damage to aging and to various disease states date back only to the 1940s. Johan Bjorksten, a research chemist working for a branch of Eastman Kodak, first observed a similarity between the aging of film materials and the aging of human tissues in 1941. He surmised that the common point is the damage to both by free radicals and that in living organisms this damage results in the cross-linking of protein molecules, including the RNA and DNA strands which reproduce all the proteins in the body. In the 1950s Denham Harman of the University of Nebraska put theory into practice by experimenting with the addition of antioxidants and other free radical deactivators to the diets of laboratory mice. His trials resulted in dramatically increased life spans for his experimental animals. These results often have been duplicated and even surpassed, which is good. However, the success of the antioxidant theory sometimes leads us to overlook what are often the more significant roles of nutrients that just happen to be antioxidants. Vitamin E is but one example of this, as scientists are only belatedly coming to realize. The most powerfully health supportive members of the family apparently are not always the ones that are the best antioxidants. This is important news for anyone who supplements with vitamin E or who should be supplementing with this vitamin.

The term "vitamin E" refers to a family of at least eight related fat-soluble antioxidant compounds. The tocopherol (considered to be the true vitamin E) and tocotrienol subfamilies are each composed of alpha-, beta-, gamma- and delta-forms having unique biological effects. New forms of both families have recently been found. Vitamin E is produced by many different plant species and is usually found concentrated in the seed, the germ and other oil-bearing fractions. Alpha-tocopherol, as in d-alpha-tocopheryl succinate and d-alpha-tocopheryl acetate. In terms of antioxidant benefits, it is now clear that natural is better and that the most commonly supplemented form of vitamin E is not the best. Several studies have shown that natural vitamin E may be up to twice as bioactive as the same amount of the synthetic form. Moreover, our bodies easily distinguish between them. One animal study found that supplementation with natural vitamin E resulted in an approximately twofold higher plasma alpha-tocopherol concentration than did use of the synthetic vitamin. Studies using yet other markers for bioactivity suggest that natural E may be more than three times as potent as synthetic E.

The Vitamin E Family—

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CoA reductase, a key enzyme in the synthesis of cholesterol. For lowering total and LDL cholesterol levels, gamma-tocotrienol has the best evidence. Important antiproliferative and neuroprotective effects that may be independent of antioxidant activity also have been demonstrated.

It is these antioxidant-independent benefits of the tocopherols and the tocotrienols that are capturing attention increasingly. Indeed, as one review paper has put it, "many molecules have the ability to chemically scavenge free radicals and thus act in the test tube as antioxidant, but their main biological function is by acting as hormones, ligands for transcription factors, modulators of enzymatic activities or as structural components." (Curr Med Chem. May 2004. Vol. 11(9) pp. 1113–33.) With regard to the tocopherols, such functions include inhibition of inflammatory pathways, for instance, those involving 5-lipoxygenase and phospholipase A2. Alpha-tocopherol, for instance, has been shown to inhibit cell proliferation, platelet aggregation and monocyte adhesion—all of which are non-antioxidant benefits.

Now scientists are discovering that not only are many of the E family's benefits not related to antioxidant functions, but as indicated earlier, these benefits are actually stronger in the so-called lesser members of the family. Research has shown that gamma-tocopherol is metabolized more efficiently by the body than is alpha-tocopherol. When both forms of vitamin E are taken together, the water-soluble metabolite of gamma-tocopherol appears more quickly in the blood. Similarly, gamma-tocopherol is selectively taken up by cells and removed from plasma more rapidly than is alpha-tocopherol.

Gamma-tocopherol may be particularly important for supporting immune functioning. Gamma-tocopherol appears to play a significant role in modulating intracellular antioxidant defense mechanisms. Macrophages in one study showed a greater uptake of gamma-tocopherol compared to alpha-tocopherol. In addition, the presence of gamma-tocopherol promoted the cellular uptake of alpha-tocopherol. Moreover, gamma-tocopherol and its major metabolite, in contrast to alpha-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. In animal trials, it was gamma-tocopherol rather than alpha-tocopherol that demonstrated a powerful anti-inflammatory effect. Researchers attribute this to an inhibition of COX-2 (cyclooxygenase-2) activity.

There is even more to the picture than that. Although gamma-tocopherol is a weaker physiological antioxidant than is alpha-tocopherol, in a trial investigating cell growth, gamma-tocopherol more strongly regulated proper cell proliferation and provided for more accurate DNA synthesis than did alpha-tocopherol. In another investigation of the impact of tocopherols on prostate cancer cell proliferation, gamma-tocopherol proved to be much more powerful than alpha-tocopherol. These trials, as is true of others, indicate that non-antioxidant mechanisms are responsible for some of the superior benefits of gamma-tocopherol.

Another overlooked member of the vitamin E family is delta-tocopherol. Recent research suggests that delta-tocopherol, followed by gamma-tocopherol, is the most stable of the vitamin E isomers and for some purposes the most effective under low oxygen conditions. Moreover, some research with breast cancer cells has demonstrated inhibition of proliferation by delta-tocopherol and the tocotrienols, but not by the other tocopherols. Yet again, the mechanisms involved were non-antioxidant molecular mechanisms.

At the cellular level, vitamin E acts by inhibiting smooth muscle cell proliferation, platelet aggregation, monocyte adhesion, the uptake of oxidized LDL and cytokine production, all effects which are not the result of the antioxidant activity of the tocopherols, but rather of targeted molecular actions of this family of compounds. Likewise, the tocopherols influence the activity of several key enzymes that affect pathways involving COX-2, 5-lipoxygenase, nitric oxide synthase, superoxide dismutase, etc. In living animals, gamma-tocopherol probably is the most active member of its family, but certain important benefits seem to depend upon alpha- and delta-tocopherol, as well. There is an overlap between the tocopherols and the tocotrienols, yet the latter members of the E family exert much more powerful signaling functions involving the regulation of total and LDL cholesterol levels and some types of cancers. The last decade of research into the whole vitamin E family, therefore, shows that we need to go beyond looking at E as merely an antioxidant. To obtain the full benefits of vitamin E, supplementation should more closely follow the path found in nature: gamma-tocopherol should predominate and the entire E family of tocopherols and tocotrienols should be represented as nature intended.

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