

# The Free Radical Fantasy

## A Panoply of Paradoxes

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**ABSTRACT:** Overly exuberant and exaggerated past expectations and claims of the free radical theory have been quieted by extensive randomized, double-blind, controlled human studies. A half century of data demonstrates its lack of predictability and it has not been validated by the scientific method. Widespread use of antioxidants has failed to quell the current pandemic of cancer, diabetes, and cardiovascular disease or to stop or reverse the aging process. Electronically modified oxygen derivatives contribute to the modulation of cellular redox status, which is of primary importance in disease prevention and homeostasis.

**KEYWORDS:** oxidants; antioxidants; redox; free radical theory; aging; anti-aging, vitamins

### INTRODUCTION

The basis for the free radical theory of Harman<sup>1</sup> is the belief that oxygen free radicals produce harmful oxidation products, which randomly accumulate with aging, and that they are responsible for more than 100 diseases and aging. This theory was further extended to especially apply to redox damage of the mitochondrion.<sup>2</sup>

Inherent in the free radical theory was the concept that the harmful effects of oxidized products could be diminished or alleviated by the judicious use of antioxidants. Although there was initially widespread enthusiasm for the antioxidant studies, it has become apparent, after 50 years of investigation, that the overall analysis of the data has failed to conclusively validate or confirm the free radical theory. The dream of stopping the aging process or of wiping out hordes of diseases with the use of antioxidants has turned into a meta-analytic nightmare for the sycophants of the free radical theory.

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**Ann. N.Y. Acad. Sci. 1067: 22–26 (2006). © 2006 New York Academy of Sciences.  
doi: 10.1196/annals.1354.004**

Paradoxes are everywhere. Not only have antioxidants failed to stop disease and aging but also they may cause harm and mortality, which precipitated the stoppage of several large studies. A 2005 nutrition and supplement review in *JAMA* bolsters my position.<sup>3</sup> In my opinion, this scenario exemplifies the rise and fall of the free radical theory.

The following antioxidant studies have been conducted on more than 550,000 humans and have failed to lend credence to the free radical theory.

*Alpha-Tocopherol/Beta-Carotene Cancer Prevention Study (ATBC) (1994)*<sup>4</sup>: a study of pooled Finish male smokers (29,133 in all) found an 18% excess of lung cancer in participants receiving beta-carotene after 6 years and increased the incidence of cardiac death, hemorrhagic stroke, and the risk for major coronary events. This trial was stopped early.

*Polyp Prevention Study Group (1994)*<sup>5</sup>: Seven hundred and fifty-one patients completed this 4-year clinical trial. Neither  $\beta$ -carotene or vitamins C and E reduced the incidence of adenomas nor prevented any subtype of polyp.

*The Beta-Carotene and Retinol Efficacy Trial (CARET) (1996)*<sup>6</sup>: Smokers, former smokers, and workers exposed to asbestos (18,314) were given  $\beta$ -carotene and vitamin A for 4.0 years, and they had a 28% increase in lung cancer incidence. The trial was stopped 21 months early.

*Physicians' Health Study I (PHS I) (1996)*<sup>7</sup>:  $\beta$ -carotene, given to 22,071 U.S. male physicians, showed no differences in the incidence of malignant neoplasms, stroke, or cardiovascular disease or in overall mortality after 12 years of supplementation.

*ATBC Substudy (1997)*<sup>8</sup>: Men with prior myocardial infarction (1,862) took alpha-tocopherol and  $\beta$ -carotene for 5.3 years. There were no significant differences in major coronary events, but significantly more deaths from fatal coronary heart disease.

*Antioxidant Vitamin Effect on Traditional CVD Risk Factors (1997)*<sup>9</sup>: In 297 retired teachers, after 2–4 months of combined antioxidant supplements, showed no significant effect on systolic and diastolic blood pressures, fasting serum lipids (total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) and fasting glucose.

*The Nurses' Health Study (1998) and Folic Acid and Colon Cancer (1998)*<sup>10</sup>: Women (88,756) taking vitamin C and  $\beta$ -carotene for 8 years did not have any reduction in heart disease risk. Multivitamins containing folic acid had no benefit with respect to colon cancer after 4 years of use and had no significant risk reductions after 5 to 9 or 10 to 14 years of use. Long-term use of multivitamins (for more than 15 years) may substantially reduce risk for colon cancer, perhaps on account of folic acid.

*The Women's Health Study (1999)*<sup>11</sup>: In 39,876 healthy women aged 45 years or older, there was no benefit from  $\beta$ -carotene, after 4.1 years, on the incidence of cancer, cardiovascular disease, or mortality.

*The GISSI Trial (1999)*<sup>12</sup>: Patients (11,324) with recent heart attacks showed no benefit from vitamin E supplements for up to 2 years. Results indicated that n-3 PUFA supplements, but not synthetic vitamin E, reduced long-term complications of myocardial infarction. The fish oil group had 15% decreased risk of death, nonfatal MI, and stroke.

*The Health Professionals Follow-Up Study (1999)*<sup>13</sup>: In this study 43,738 men were followed for 8 years. Vitamin E and C supplements and specific carotenoids did not reduce risk for stroke.

*Meta-Analysis of Vitamin E in CVD, Ischemic Heart Disease (IHD), and Mortality (2000)*<sup>14</sup>: Four randomized trials on 51,000 participants taking vitamin E or placebo for 1.4 to 6 years did not demonstrate a reduction in cardiovascular and IHD mortality or nonfatal myocardial infarction.

*The Heart Outcomes Prevention Evaluation Study (HOPE) (2000)*<sup>15</sup>: In this study 9,541 patients, at high risk for cardiovascular events or diabetes, were treated with vitamin E for 4.5 years, which had no effect on cardiovascular outcomes or stroke.

*Age-Related Eye Disease Study Research Group (AREDS) (2001)*<sup>16</sup>: All the 4,757 participants taking  $\beta$ -carotene and vitamins C and E had no effect on the 7-year risk of development or progression of age-related lens opacities or visual acuity loss.

*Antioxidant Vitamins and U.S. Physician CVD Mortality (2002)*<sup>17</sup>: Male U.S. physicians (83,639) taking vitamin E, vitamin C, or multivitamins did not show a significant decrease in total CVD or CHD mortality.

*The Women's Angiographic Vitamin and Estrogen (WAVE) Trial (2002)*<sup>18</sup>: Four hundred and twenty-three postmenopausal women, with at least one 15% to 75% stenosis in the coronary artery, showed that neither HRT nor antioxidant vitamin supplements (vitamins C and E) provided any cardiovascular benefit. Instead, a potential for harm was suggested. Vitamin E supplements provided no benefit for cardiovascular mortality as reported in a 2003 review by Vivekananthan *et al.*<sup>19</sup>, which included seven trials with 82,000 patients. A meta-analysis conducted in 2005, including more than 135,000 subjects, concluded that high doses of vitamin E increased mortality.<sup>20</sup>

The British Heart Protection Study, following 20,000 subjects for 5 years, found no benefit from a combination of vitamins E and C, and  $\beta$ -carotene, for heart disease, cancer, and several other conditions.<sup>21</sup> A study of more than 20,000 subjects found that vitamin E, vitamin C, and  $\beta$ -carotene supplementation resulted in small but significant increases in serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations.<sup>22</sup>

Hopefully, for open-minded investigators, my point is made.

## CONCLUSION

Randomized, double-blind, controlled trials in humans, which are the clinical “gold standard,” have repeatedly shown that the free radical theory lacks predictability and fails to be confirmed by the scientific method.

Admittedly, there were likely many confounding variables in the antioxidant studies involving the use of other drugs, use of other dietary supplements, varying diets, varying environmental factors, presence or lack of exercise, degrees of obesity, varying dosage levels, varying antioxidant combinations, synthetic or natural vitamin sources, improperly combined study groups, use of improper exclusion criteria, flawed statistical methods, overgeneralization of findings, etc. Even though one can find positive antioxidant studies, the overall lack of predictability is undeniable.

I have formulated a new pro-oxidant protective paradigm to explain disease allowance and to stimulate new thinking regarding treatment.<sup>23,24</sup> Electronically modified oxygen derivatives (EMODs) support modulation of redox cycling and redox status, which are of utmost importance for disease prevention and maintaining cellular homeostasis.

In conclusion, extensive antioxidant studies have failed to confirm the free radical theory and antioxidant use may cause harm or accelerate one’s demise. The free radical theory has fallen.

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