# Chapter 6. Future Research

One outcome of this analysis is the discordant results between the observational data, which suggest that foods high in the selected antioxidants are beneficial, and the majority of the research presented here on supplemental antioxidants. These discordant results could occur for at least two reasons.

The tested antioxidant supplements do not contain the agents responsible for the benefit reported in observational studies.

The observational studies of food consumption are confounded by some other factor that is responsible for the effect. The recent failure of hormone replacement therapy to achieve in an RCT the cardiovascular benefit reported in observational studies has been attributed to confounding in the observational studies, demonstrating that no matter how well designed and how often replicated, confounding must always be considered a possibility.

Therefore, it would seem to us that the thrust of new research into antioxidants and CVD should be randomized trials. These RCTs should consider the following:

Use supplements that are standardized in terms of dose, source and stereoisomers;

Measure clinical outcomes (that include death, MI, hospitalization, quality of life, exercise tolerance, etc.) in addition to intermediate outcomes (levels of antioxidants, blood lipid levels, etc.);

Be conducted over a sufficiently long period of time to see an effect (on the order of years);

Enroll heterogeneous populations so that the results may be extrapolated to the US population (most existing studies have enrolled only or predominantly Caucasian participants).

Such studies may also want to consider:

Testing interventions that have constituents that more closely mimic the chemical constituents of the foods reported to have protective benefits.

Assessing whether any agreement can be reached among exports in the field regarding dose and formulation so that in the event no benefit is observed in the trial the study will not be subject to post hoc criticism that inadequate doses and/or formulations were tested.

Assessing whether patients should be selected for the trial on some basis other than presence of CVD or risk factors for CVD. For example, it has been proposed that antioxidants may be most beneficial in subjects with low levels of antioxidants and/or have high oxidative stress.

No doubt such RCTs will be expensive to conduct and take years to produce their results. However, the pay off for successful completion of such a trial is usually a definitive answer to a clinical question (for example, the MRC/BHF study, the HOPE study, the HERS trial,[194] and the ALLHAT[195] study).

With regard to what antioxidant supplements study, the results reported here leave us less than enthusiastic about vitamin E or vitamin C as individual agents having any substantial clinical benefit. There have been several trials of coenzyme Q10 that report favorable clinical

outcomes other than death, but methods or reporting problems preclude us drawing conclusions. Of note, coenzyme Q10 is the only one of the three supplements we assessed not to have been subjected to a major RCT enrolling thousands of patients. Consideration must also be given to ongoing trials of antioxidants, in order to avoid repetition. Identifying all of these and their expected completion dates was beyond the scope of this study, but must be known to experts in the field, such as those who would be assembled by NCCAM to make recommendations about a research agenda.

Lastly, independent of the above, something in the observational studies was associated with substantial cardiovascular benefit, and a careful study of the behaviors of individuals who consume fruits and vegetables containing antioxidants may also be worthwhile."