Oxidant stress in cardiovascular disease: an emerging modality or a disproved theory?

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Heard melodies are sweet, but those unheard
Are sweeter; therefore, ye soft pipes, play on.
John Keats

Free radical catalyzed damage to lipids, protein and DNA has been broadly implicated as a mechanism of disease. This is true for cardiovascular disease[1] as well as a range of neurodegenerative diseases and cancer. Despite much work on radical generation and evidence for direct radical catalyzed tissue injury, the few large scale clinical trials of antioxidants in cardiovascular disease have been disappointing. While some have lent encouragement to an antioxidant strategy[2,3], others[4,5], including, most recently, the Heart Protection Study (presented at the 74th Scientific Session of the American Heart Association, Anaheim, CA, USA, 2001) have failed to substantiate a cardiovascular benefit from dietary supplementation with antioxidant vitamins. How does one explain this conundrum?

Most obviously, there may be no relevance of free radical based mechanisms to the endpoints of the trials reported to date. Perhaps oxidant stress is of relevance to atherogenesis[6,7], but not to the clinical complications of plaque instability, myocardial infarction and cardiovascular death, which were measured in these trials. Estimates of dietary content of antioxidant vitamins have varied inversely with these clinical endpoints[8,9], but such retrospective epidemiological analyses may be confounded by other covariates of a healthy lifestyle. Secondly, the trials may have failed because the vitamins employed are poor pharmacological probes for the mechanism under consideration. Adverse, prooxidant effects of vitamin C and vitamin E are well documented *in vitro*[10,11] and beta-carotene consumption has been related to accelerated tumor progression in a clinical trial[12]. Recently, the beneficial effects of hypolipidemic drugs on circulating HDL have been adversely impacted by combination with antioxidant vitamins[13]. Finally, vitamin E is a quite inefficient antioxidant[14]; even in appropriate settings, tolerated doses in humans may give incomplete protection against the consequences of oxidant stress.

Despite the advances in basic research relating to oxidant stress, clinical investigation is only now coming of age with the emergence of quantitatively accurate estimates of the consequences of lipid peroxidation[15,16]. Several contributions in this supplement relate to such methodology and the insight it affords to our understanding of mechanism in cardiovascular disease. Oddly, none of the clinical trials of antioxidant vitamins performed to date have included any measurements that indicated that the doses selected were actually suppressing any indices of oxidant stress *in vivo*. Furthermore, no indication was provided that the individuals under study were susceptible to intervention with an antioxidant. For example, studies *in vitro* have shown that the response to an exogenous antioxidant is critically dependent on depletion of the remarkably diversified systems of antioxidant defense. In humans, we know that doses of vitamin E, that suppress elevated levels of isoprostanes – indices of lipid peroxidation – in diseased individuals with depleted antioxidant defense[17-20], have no effect on normal isoprostane levels in healthy volunteers[21,22]. Inclusion of such unsusceptible individuals would seriously undermine sample size calculations in studies of the antioxidant effects of vitamin E.

The development of quantitatively accurate indices of lipid peroxidation has contributed substantially to clinical research in this area. However, comparative indices of free radical catalyzed damage to proteins and DNA are only now beginning to emerge and we have no data which integrate the impact of pro- or antioxidant manipulations on contemporary indices of oxidative damage to proteins, lipids and DNA. As indicated by the contributions to this minisymposium, our insights into the role of oxidant stress is beginning, rather than concluding with the outcome of these clinical trials.

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