

(copper, zinc, manganese) as shown in Figure 9.4. Multiple nutritional factors may afford protection from oxidative damage.<sup>55</sup> For example, magnesium deficiency may enhance hydrogen peroxide production and oxidative damage.<sup>56</sup> Adaptive systems can increase rates of enzyme synthesis, especially those required for glutathione production.<sup>57</sup> Laboratory evaluations are available that allow assessment of the current rate of oxidative damage and the adequacy of antioxidant protection against further damage. Markers of oxidant damage to fatty acids (membranes), proteins and DNA are available as well as various indicators of overall or specific antioxidant protection.

#### REFER TO CASE ILLUSTRATION 9.1

### **Vitamins A, C and E and $\beta$ -Carotene**

Laboratory evaluations for these nutrients are discussed in Chapter 2. They all play critical roles in the chain of electron acceptors that allows removal of oxygen radicals. Vitamin A and its precursor  $\beta$ -carotene have independent actions in this process, and the various isomers of tocopherol likewise operate with redox potentials uniquely beneficial to specific tissues.

Vitamins C and E are major players in antioxidant protection. The clinical value of  $\beta$ -carotene testing may be as a marker of good dietary habits rather than as a direct indicator of antioxidant status, since it may be an insignificant factor in free radical protection.<sup>58</sup>

Profiling fat-soluble vitamins in serum has been reviewed in Chapter 2. Such testing provides direct concentration measures for vitamins A and E, along with  $\beta$ -carotene and coenzyme Q<sub>10</sub>. These are the principal molecules examined for deficiencies to reveal need for augmenting dietary intake. More comprehensive profiles are available that include the various minor isomers of vitamin A (carotenoids) and vitamin E (tocopherols).

### **Isoflavones**

The polyphenolic isoflavones, such as genistein and daidzein found in soy, have extensive antioxidant properties. Because they undergo extensive metabolism in the intestine, however, as discussed in Chapter 6, "Organic Acids," it is not possible to infer systemic antioxidant contributions from their *in vitro* properties. Antioxidant potentials measured for the common products that are absorbed after bacterial metabolism suggest

substantial biological antioxidant activity in individuals who regularly consume isoflavones-rich foods.<sup>59</sup> Plasma antioxidant status, homocysteinemia and endothelial response have been shown to be improved by increasing dietary isoflavone intake.<sup>60-62</sup> Other dietary polyphenols such as the catechins, may contribute appreciable antioxidant protection also.<sup>63</sup>

### **Copper, Manganese, Selenium, Zinc and Riboflavin**

Copper, manganese, selenium, zinc and riboflavin are considered antioxidant nutrients because they play specific roles as cofactors for the enzymes that catalyze reactions that remove oxygen radicals. These nutrients are cofactors (or precursor vitamins) for the enzymes glutathione reductase (FAD),<sup>64</sup> glutathione peroxidase (Se),<sup>65</sup> and superoxide dismutase (Cu, Mn, Zn).<sup>66</sup> Total-body selenium is so largely dedicated to this role that some studies have evaluated overall oxidative protection by measuring serum and urinary selenium along with red cell enzymes.<sup>67</sup> Laboratory evaluations and specific metabolic roles for the antioxidant trace elements are discussed in Chapter 3, "Nutrient and Toxic Elements."

### **Can Antioxidant Supplements Be Dangerous to Health?**

The "Of Further Interest" box on the following pages deals with the issue of poorly designed studies that can raise unnecessary questions about the safety of antioxidant supplementation in clinical practice. The particular report addressed there drew questionable conclusions that led to news headlines such as "Antioxidants Increase All-Cause Mortality."

Before presenting data that suggest real dangers, and at the risk of stating the obvious, a practical note may be worthy. Treating individual patients who have nutrient insufficiencies demonstrated by laboratory evaluations is not in any way comparable to population-based studies that examine average outcomes of disease incidence. A great many published studies use a design of supplementing subject and control populations without any qualification of the participants' initial nutrient status. This approach derives frequently from the misplaced focus on the curing of disease by simply increasing nutrient intake. Such results are categorically irrelevant to the common sense interventions to correct demonstrated nutrient deficiencies in patients with diseases (to aid recovery) or without them (to reduce risk of