5. Other Beneficial Effects

A number of carotenoids are being evaluated for health benefits other than cancer prevention. In this section, the scientific evidence in support of other potential health effects of carotenoids and the potential mechanisms involved is discussed.

5.1 Photosensitivity disorders

Carotenoids, including β-carotene and to a lesser extent canthaxanthin, have been used successfully in the treatment of certain photosensitivity diseases for more than 25 years. This clinical application derived from the recognition that carotenoids protect photosynthetic bacteria, algae and green plants against photosensitization (Mathews-Roth, 1987). As reviewed elsewhere (Mathews-Roth, 1993), most patients with the genetic disease, erythropoietic protoporphyria, benefit from high doses of supplementation with β-carotene and/or canthaxanthin. The recommended dose of β-carotene for adults with erythropoietic protoporphyria is about 180 mg/d—substantially higher than the doses investigated for cancer prevention (15–50 mg/d). Despite these relatively high doses, some patients with erythropoietic protoporphyria do not respond to carotenoid therapy, either because of poor absorption of the carotenoids or because of markedly elevated blood porphyrin concentrations. No serious side-effects of high doses of β-carotene supplements have been reported in such patients, and no long-term toxicity has been observed.

Erythropoietic protoporphyria is a disease of porphyrin metabolism, characterized by abnormally elevated concentrations of protoporphyrin (Mathews-Roth, 1987), which acts as an endogenous photosensitizer. As carotenoids can interact and quench photosensitizer triplet states and singlet oxygen, their efficacy in this disorder appears to be a consequence of the quenching of excited species.

Because of the therapeutic efficacy of β-carotene for erythropoietic protoporphyria, it has been evaluated for use in other photosensitivity diseases. For example, Kornhauser *et al.* (1990) evaluated the ability of β-carotene to protect against psoralen-induced phototoxicity in a murine model. β-Carotene reduced the prevalence of erythema in this model, despite relatively low dermal concentrations after its oral administration. High doses of β-carotene have also been evaluated for the prevention of sunlight-induced erythema, but the observed protective effects were too small for it to be recommended for the prevention of sunburn (Mathews-Roth *et al.*, 1972; Garmyn *et al.*, 1995).

5.2 Cardiovascular disease

The results of descriptive, cohort and case–control studies suggest that carotenoid- and/or β-carotene-rich diets may prevent cardiovascular disease, as reviewed elsewhere (Gaziano & Hennekens, 1993; Manson *et al.*, 1993; Kohlmeier & Hastings, 1995). In a biochemical epidemiological study of plasma carotenoids (the vitamin substudy of the WHO/MONICA Project), plasma was obtained from about 100 healthy males at each of 16 study sites in Europe for analyses of antioxidant nutrients. The median antioxidant nutrient concentrations were then compared with the mortality rates from concurrent, age-specific ischaemic heart disease in the 16 study populations. The results showed a striking inverse correlation between those rates and plasma vitamin E concentrations (r^2 = 0.63). A similar comparison between the median plasma β-carotene concentrations and the rate of mortality from ischaemic heart disease revealed no association when all 16 study sites were considered (r^2 = 0.04), but a reasonably strong inverse association (r^2 = 0.50) when three study sites, all apparent outliers and all Finnish, were excluded from the analysis (Gey *et al.*, 1993a).

In a prospective study in Basel, Switzerland, men who had low concentrations of β-carotene and vitamin C in their blood were at a significantly increased risk for subsequent ischaemic heart disease (RR, 1.96; p = 0.022) and stroke (RR, 4.17; p = 0.002) (Eichholzer *et al.*, 1992; Gey *et al.*, 1993b). Total serum carotenoids, measured at baseline in the placebo group of a trial on the primary prevention of coronary disease, were inversely related to subsequent coronary heart disease. Men in the highest quartile of total serum carotenoid concentrations had an adjusted relative risk of 0.64 (95% CI,

0.44–0.92); the relative risk among men who had never smoked was 0.28 (95% CI, 0.11–0.73) (Morris *et al.*, 1994). In a nested case–control study of serum antioxidant nutrients and subsequent myocardial infarct in a cohort study in Washington County, Maryland, USA, the risk for myocardial infarct was inversely associated with serum β-carotene concentration (*p* value for trend = 0.02). When the data were stratified by smoking status at the time blood was drawn, the excess risk associated with low serum concentrations of β-carotene, lycopene, lutein and zeaxanthin was confined to current smokers (Street *et al.*, 1994). Plasma carotene concentrations were significantly inversely related to the risk for angina pectoris, but the relationship was no longer statistically significant after adjustment for smoking (Riemersma *et al.*, 1991).

A different biochemical approach was used to quantify β-carotene status: β-carotene concentrations were measured in adipose tissue samples collected by needle aspiration from the buttocks of 683 people with myocardial infarct and 727 age-matched controls. The risk for myocardial infarct, adjusted for age, smoking and body mass index, in the lowest quintile of adipose β-carotene concentrations as compared with the highest was 1.78 (95% CI, 1.17-2.71); the risk was primarily confined to current smokers (odds ratio, 2.39; 95% CI, 1.35–4.25; versus an odds ratio of 1.07 for nonsmokers) (Kardinaal *et al.*, 1993). In a large, multicentre case–control study of acute myocardial infarct, trend analyses showed that the adipose tissue concentrations of β-carotene, α-carotene and lycopene were inversely associated with risk when modelled separately; however, the carotenoid concentrations were highly correlated, and when they were included simultaneously in the model, lycopene had the greatest protective effect (Kohlmeier *et al.*, 1997).

Of the studies in which diet was used to estimate β-carotene status, the study of US health professionals showed protective effects of dietary carotene, with a relative risk for coronary heart disease of 0.71 (95% CI, 0.55–0.92) for people in the top quintile of total carotene intake (> 19 034 IU/d) relative to the lowest quintile of intake. Smoking modified the effect: the relative risk was 0.30 (95% CI, 0.11–0.82) among current smokers, 0.60 (95% CI, 0.38–0.94) among former smokers and 1.09 (95% CI, 0.66–1.79) among nonsmokers (Rimm *et al.*, 1993). Similar protective effects of dietary β-carotene were seen in the cohort of nurses, with a relative risk of 0.78 (95% CI, 0.59–1.03) for those in the top quintile of total β-carotene intake relative to those in the lowest quintile (Manson *et al.*, 1991). In contrast, a prospective cohort study of postmenopausal women showed that dietary intake of carotenoids was not associated with the risk for death from coronary heart disease in multivariate models (Kushi *et al.*, 1996). A study of the association between dietary carotenoid intake and coronary mortality in a Finnish cohort of men and women showed that dietary carotenoid (primarily β-carotene) intake was not associated with risk in men, and there was only a suggestion of an inverse association in women (Knekt *et al.*, 1994).

Epidemiological studies of cardiovascular disease, much like those of cancer, now often involve the use of intermediate end-points. One such end-point is the thickness of the intima media, which can be estimated by ultrasonography, as a measure of atherosclerosis. This method has been used to examine the relationship between atherosclerosis and antioxidant status. A progressive decrease in the thickness of the intima media on the common carotid arteries was found with increasing concentrations of total plasma carotenoids in both men and women. The association disappeared, however, after adjustment for potential confounders, most notably body mass index (Bonithon-Kopp *et al.*, 1997). In another study, progression of the thickness of the intima media was 92% greater in the lowest versus the highest quartile of plasma β-carotene concentrations (Salonen *et al.*, 1993).

The finding in numerous observational studies that increased intake of carotenoid-containing diets and higher blood concentrations of carotenoids are associated with reduced risks for cardiovascular disease cannot be interpreted as a specific protective effect of β-carotene or other carotenoids *per se*; that type of evidence can best be obtained by randomized trials.

Some of the first such studies were early analyses of 333 men enrolled in the Physicians' Health Study who were known to have stable angina or to have undergone coronary revascularization. In a preliminary report, subjects who received supplemental β-carotene (50 mg every other day) for five years had a 51% reduction in the risk for major coronary events and a 54% reduction in the risk for major vascular events (Gaziano, 1994). In a subsequent report on the same group of men, however, those assigned to β-carotene had a nonsignificant increase in the risk for death from cardiovascular disease (RR, 1.33; 95% CI, 0.78–2.26) (Gaziano *et al.*, 1996; see also section 7.1).

In the full population of the Physicians' Health Study, 12 years of supplementation with β-carotene (50 mg every other day) had no significant effect on the risk for cardiovascular disease (Hennekens *et al.*, 1996). In a trial for the prevention of oesophageal and gastric cancer in the general population in Linxian, China, the combination of β-carotene, vitamin E and selenium resulted in a 10% reduction in mortality due to cerebrovascular disease (RR, 0.90; 95% CI, 0.76–1.07), this disease accounting for about 25% of all deaths in this population (Blot *et al.*, 1993). In people with oesophageal dysplasia, supplementation with a multivitamin–multimineral preparation plus 15 mg β-carotene reduced the rate of mortality from cerebrovascular disease by 37% (RR, 0.63; 95% CI, 0.37–1.07; Mark *et al.*, 1996). The decrease was greater for men (RR, 0.42) than for women (RR, 0.93) (Li, J.-Y. *et al.*, 1993).

The results of the ATBC and CARET trials with regard to cardiovascular disease suggest a possible harmful role of supplemental β-carotene and are considered elsewhere (see section 7.1). In the Skin Cancer Prevention Study, participants whose blood concentrations of β-carotene were highest when they were randomized had the lowest risk for death from cardiovascular disease in the succeeding 10 years (RR, 0.57; 95% CI, 0.34–0.95); however, there was no evidence that β-carotene supplementation had any effect on mortality from these diseases (RR, 1.16; 95% CI, 0.82–1.64) (Greenberg *et al.*, 1996).

5.3 Age-related macular degeneration and cataract

Dietary carotenoids may be important in the prevention of two ocular conditions — age-related macular degeneration and senile cataract. The macula is a small, yellow region in the centre of the retina. Degeneration of the macula is the most common cause of irreversible blindness in people over the age of 65 (Seddon *et al.*, 1994a; Snodderly, 1995). Cataracts are also problematic, cataract extraction being the most frequently performed surgical procedure among the elderly. While the causes of these conditions are not known, oxidative processes may play a role. Cataracts are thought to result from photo-oxidation of lens proteins, which results in protein damage, accumulation, aggregation and precipitation in the lens (Taylor, 1993). The cornea and lens filter out UV light, but visible blue light reaches the retina and may contribute to photic damage and other oxidative insults (Seddon *et al.*, 1994a). Carotenoids might interfere with both processes.

The potential role of carotenoids in the prevention of age-related macular degeneration has been reviewed (Snodderly, 1995); this section is therefore not comprehensive but highlights key studies in this area. In a study of dietary intervention, an inverse association was found between the consumption of carotene-rich fruits and vegetables and the risk for age-related macular degeneration, on the basis of data from the first National Health and Nutrition Examination Survey in the USA (Goldberg *et al.*, 1988). The association between carotenoid intake and advanced age-related macular degeneration was addressed in a large, multicentre case–control study involving 356 cases and 520 control subjects with other ocular conditions. Patients with this condition who were in the highest quintile of carotenoid intake had a 43% lower risk for macular degeneration than those in the lowest quintile (odds ratio, 0.57; 95% CI, 0.35–0.92). Intake of lutein and zeaxanthin (grouped in the carotenoid food composition database) was most strongly associated with the reduced risk. Increased consumption of spinach and collard greens, which are rich dietary sources of lutein and

zeaxanthin, was also associated with a significant reduction in risk (Seddon *et al.*, 1994a). It is biologically plausible that lutein and zeaxanthin have protective effects against macular degeneration, as these carotenoids selectively accumulate in the macula (Bone *et al.*, 1988; Handelman *et al.*, 1988) and account for the yellow colour observed in this region of the retina. For unknown reasons, zeaxanthin is the dominant carotenoid at the centre of the fovea, whereas lutein dominates outside the foveal centre (Bone *et al.*, 1988). The specificity of incorporation of carotenoids into the macula may give some clues as to their role in the prevention of age-related macular degeneration.

Studies in which blood carotenoid concentrations were used as the measure of exposure also suggest protective effects against the risk for age-related macular degeneration. For example, in one case–control study, serum carotenoid concentrations were measured in 391 patients with neovascular age-related macular degeneration and 577 controls, and significant protective effects were reported for total carotenoids, β-carotene, α-carotene, cryptoxanthin and lutein/zeaxanthin, with odds ratios ranging from 0.3 to 0.5 for people in the 80th percentile or higher versus those in the 20th percentile or lower. Serum lycopene was not, however, protective in this study (odds ratio, 0.8; $p = 0.4$) (Eye Disease Case–Control Study Group, 1993). In contrast, an association was found only between the serum concentration of lycopene and age-related maculopathy in 167 case–control pairs drawn from a study in the USA, persons in the lowest quintile of lycopene concentration having a doubling in risk for maculopathy (Mares-Perlman *et al.*, 1994). In a study of ageing in Baltimore, USA, the relationship between plasma β-carotene concentration and age-related macular degeneration was studied in 226 patients. A non-significant inverse relationship was found (odds ratio for high quartile versus low, 0.62). Plasma lutein and zeaxanthin were not measured (West *et al.*, 1994). In a fourth study, no relationship was found between the plasma concentrations of α-carotene, β-carotene, β-cryptoxanthin, lutein and lycopene and the occurrence of age-related maculopathy; however, the sample size was limited to 65 matched pairs (Sanders *et al.*, 1993).

New techniques are now available for measuring the optical density of retinal carotenoids (macular pigment) by noninvasive methods (see, e.g. Hammond & Fuld, 1992), which may provide a long-term measure of carotenoid status in this tissue, facilitating future epidemiological studies.

In the ATBC cancer prevention trial, a random sample of 990 participants were examined ophthalmologically at the end of the trial, and 66 cases of age-related macular degeneration were observed in the group receiving β-carotene versus 51 in those given placebo (difference not significant) (Teikari *et al.*, 1995).

The literature on antioxidant nutrients and cataract has also been reviewed (Taylor, 1993; Taylor *et al.*, 1995). Higher dietary intake of carotenoids or higher blood concentrations of carotenoids have been found to prevent various forms of cataract in some but not all studies. For example, subjects with low plasma carotenoid concentrations (< 20th percentile) had a 5.6-fold increased risk for any senile cataract and a 7.2-fold increased risk for cortical cataract when compared with subjects with high plasma carotenoid concentrations (> 80th percentile) (Jacques & Chylack, 1991). A cross-sectional analysis of serum α-carotene, β-carotene, lutein/zeaxanthin, lycopene and β-cryptoxanthin concentrations and the severity of nuclear and cortical opacities showed that higher concentrations of individual or total carotenoids were not associated overall, but higher serum β-carotene was protective in men and higher concentrations of α-carotene, β-cryptoxanthin and lutein were protective against nuclear sclerosis in men who smoked. In women, however, higher concentrations of carotenoids were associated with an increased severity of nuclear sclerosis (Mares-Perlman *et al.*, 1995).

Use of vitamin supplements and the risk for cataract were also evaluated in the Physicians' Health Study. Users of multivitamins, but not of vitamin C or E alone, resulted in a marginally significant decreased risk for cataracts in comparison with people who did not take these supplements (RR, 0.75; 95% CI, 0.55–1.01). The lower risk associated with β-carotene supple-

mentation was seen in current and former smokers but not in people who had never smoked (Seddon *et al.*, 1994b).

[The Working Group noted that observational studies of cataracts, like those of most chronic diseases, are highly susceptible to confounding and must thus be interpreted cautiously. For example, markers of higher socioeconomic status are consistently associated with a decreased risk for cataract (Sperduto *et al.*, 1990). Since higher socioeconomic status is also associated with a higher intake of micronutrients and with vitamin supplementation, any protective effects could well be due to confounding. Thus, evidence from trials is critical in evaluating potential health effects.]

The cancer prevention trials in Linxian, China, included ocular examinations for participants in the trial on dysplasia and for a subset of participants in the trial in the general population. The combination of β-carotene, α-tocopherol and selenium did not reduce the prevalence of cataract in the general population. In the dysplasia trial, however, there was a statistically significant, 36% reduction in the prevalence of nuclear cataract among persons aged 65–74 years who received supplements of multiple vitamins and minerals plus β-carotene (15 mg/d) for six years (Sperduto *et al.*, 1993).

There is currently no convincing evidence that supplementation with carotenoids can affect the development or progression of age-related cataracts or age-related macular degeneration. While supplemental lutein and zeaxanthin may be of value for the prevention of macular degeneration, extremely few data are available on the pharmacology, pharmacokinetics and toxicity of these supplements in humans or in animals.

5.4 Other effects

Antioxidants, including β-carotene and carotenoids, have been suggested to be of value in the prevention or management of a number of chronic conditions, including rheumatoid arthritis (Heliövaara *et al.*, 1994; Comstock *et al.*, 1997), impaired cognition in the elderly (Perrig *et al.*, 1997) and ageing (Cutler, 1991).