5. Other Beneficial Effects

5.1 Conditions related to vitamin A deficiency

5.1.1 Night-blindness and xerophthalmia

Moderate deficiency in vitamin A leads to dryness of the conjunctiva of the eyes and decreased night vision, which in severe cases may proceed to irreversible blindness (Tee, 1992). It is implied by the status of retinol as a vitamin that all but the most severe forms of these conditions may be improved by administration of retinol or retinyl esters either as drugs or by dietary means (Olson, 1987; Gerster, 1997). The impact of vitamin A on other conditions of the eye, including macular degeneration and cataract, has been the subject of several studies but no significant effect related to retinol has been observed (Seddon *et al.*, 1994; Sanders *et al.*, 1993; Sperduto *et al.*, 1993; West *et al.*, 1994). In a study of 12 cases treated with vitamin A eyedrops for superior limbic keratoconjunctivitis, ten cases showed improvement, to varying extents (Ohashi *et al.*, 1988). [No systematic studies of this condition were available to the Working Group.]

5.1.2 Growth

Observations of the effect of vitamin A on early child growth are inconsistent. In a field study of 3377 Nepalese children, 12–60 months of age and without signs of xerophthalmia, the participants were given 60 000 μg retinol equivalents (RE) once every four months, or placebo (300 RE). No difference in weight gain or linear growth was observed, except for minor changes in arm circumference and muscle mass (West *et al.*, 1997). However, when xerophthalmic children given 120 000 RE or more at baseline were compared with the non-xerophthalmic children, the former had a significant increase in growth after adjustment for sex, age and measurement status. Although confirmatory studies are needed, the available data indicate that retinol influences growth only in individuals with vitamin A deficiency.

5.1.3 Cystic fibrosis

Retinol levels in plasma are decreased in some patients with cystic fibrosis (Rasmussen *et al.*, 1986). This may lead to overt signs of vitamin A deficiency such as xerophthalmia, decreased night vision or skin abnormalities, which are reversed upon treatment with retinol (Brooks *et al.*, 1990; Rayner *et al.*, 1989). In cystic fibrosis, up to 40% of the dietary retinol may pass unabsorbed and be lost with the stool and thus the patients need supplementation (Ahmed *et al.*, 1990). It has been debated whether dryness of the eye is a sign of vitamin A deficiency in these patients or a manifestation of the disease itself (Morkeberg *et al.*, 1995).

5.1.4 Psoriasis and other skin conditions

Vitamin A has been used to treat a large number of skin disorders, including severe acne (Heller & Schiffman, 1985), psoriasis and pityriasis (Winkelmann *et al.*, 1983). Due to the toxicity of retinol, a number of synthetic retinoids as well as retinal and retinoic acid have replaced retinol and its esters for the treatment of most of these conditions. Corrocher *et al.* (1989) observed a normal plasma level of retinol in psoriatic patients and Rollman and Vahlquist (1985) observed similar retinol levels in skin biopsies from 33 plaque psoriasis patients and 37 healthy control subjects.

Dihydroretinol was, however, significantly increased in samples of both affected and unaffected skin of psoriasis patients. In an open study, 30 psoriasis patients were treated with liarozole, an inhibitor of cytochrome P450-mediated retinol oxidation, for up to 12 months. There was a consistent decrease in symptoms as determined by the Psoriasis Area and Severity Index (PASI) scores with duration of treatment, reaching 87% by 12 months (Dockx *et al.*, 1995). This could indicate a higher demand for vitamin A by these patients. However, skin or serum retinol levels were not determined and thus this possibility has not been confirmed. [No placebo-controlled studies relating retinol with a decrease in PASI scores were available to the Working Group.]

5.1.5 Anaemia

Retinol may influence the uptake or use of iron in anaemic individuals who are vitamin A-deficient. In a randomized, double-blind, placebo-controlled trial, 251 pregnant women from West Java, aged 17–35 years, who had haemoglobin levels of 80–109 g/L, were randomized into four groups, given daily iron (60 mg), retinol (2.4 mg), both or placebo. The supplemented groups all improved significantly with respect to haemoglobin, packed cell volume and transferrin saturation compared with controls. Both iron-supplemented groups improved significantly with respect to serum ferritin, iron, and total iron-binding capacity, whereas retinol-supplemented groups had significantly increased serum retinol. The percentages of women who improved to a level of haemoglobin above the limit of anaemia (110 g/L) were 68%, 35%, 97% and 16%, respectively in the groups supplemented with iron, retinol, both or placebo. The authors concluded that improvement in vitamin A status may contribute to controlling anaemia in pregnant women (Suharno *et al.*, 1993).

5.1.6 Eclampsia and abruptio placentae

Two studies have reported an association between symptoms of eclampsia during pregnancy and low serum levels of vitamin A. Jendryczko and Drozdz (1989) followed 20 pregnant women from 28 weeks of gestation until four weeks after delivery. Blood samples were drawn initially and at delivery. In nine women who developed pre-eclampsia, retinol (263±38 μg/L) and vitamin E levels were significantly lower than in the remaining eleven normo-tensive subjects (396±23 μg/L, $p < 0.02$). In another study of pregnant women aged 14–25 years, retinol levels were significantly lower in seven cases with eclampsia (8.3 mg/dL) and in nine cases with symptoms of pre-eclampsia (15.3 mg/dL) than in their normotensive counterparts (24.2 mg/dL). A similar trend was observed for β-carotene and vitamin E (Ziari *et al.*, 1996). [No information was available to the Working Group on use of vitamin A intervention to prevent eclampsia.]

Retinol levels in venous blood samples from 71 pregnant women with *abruptio placentae* were significantly lower than in 86 pregnant women matched for gestational week. A weaker but overall significant trend was also observed for vitamin E and β-carotene (Sharma *et al.*, 1986). The authors noted that other vitamin deficiencies have been observed in previous studies and suggested that the condition may be caused by multivitamin deficiencies.

5.2 Infectious disease and mortality

Vitamin A is generally believed to be important for resistance to infections (Tee, 1992), but the available literature is more clear with regard to the negative relationship between vitamin A status and mortality in undernourished populations. Up to 1995, seven well documented double-blind placebo-controlled intervention studies had been reported: six showed a beneficial effect of retinol supplementation on child mortality (five were statistically significant) (Bates, 1995). It is important to note that all child mortality studies carried out so far have been conducted in populations in which vitamin A deficiency is prevalent. Moreover, while vitamin A has been shown to lower mortality, subsequent studies have demonstrated a less marked effect of vitamin A on morbidity (Glasziou & Mackerras, 1993).

In two large double-blind placebo-controlled trials in northern Ghana, the influence of vitamin A on mortality and morbidity was specifically addressed (Ghana VAST Study Team,

1993). In the mortality study, 21 906 children aged 6–90 months were randomized in 185 geographical clusters to receive either 200 000 IU retinol equivalents (100 000 IU under 12 months) or placebo, every four months. Mortality was significantly lower in the vitamin A-supplemented clusters than in the placebo clusters (ratio of mean mortality rates, 0.8; 95% CI, 0.7–1.0; $p = 0.03$). Among specific causes of death, only mortality due to acute gastroenteritis was significantly lower in supplemented clusters. There were no sex or age differences in mortality. Also the total numbers of attendances at clinics and of hospital admissions were both significantly lower in supplemented clusters. In the morbidity study, 1455 children aged 6–59 months were assigned on an individual basis to supplementation or placebo as outlined above. There were no differences in the mean daily prevalence of diarrhoea or acute respiratory infections. Of the 18 conditions monitored, only vomiting and refusing food/breast milk were significantly less common in supplemented children.

It is important to distinguish between the influence of infectious diseases on vitamin A status (Olson, 1987) and the possibility that vitamin A prevents infection. In the latter case, it is then necessary to establish the levels of vitamin A which are sufficient for our natural defence systems and to investigate whether high-dose vitamin A has additional effects on specific infections. In the Ghana study, a significant correlation between α1-acid glycoprotein or serum amyloid A, both indicators of infections, and low retinol status was observed, whereas no association was found between serum retinol levels and symptoms of infection (Filteau *et al.*, 1993). The authors' interpretation was that subclinical, underlying infections influence serum retinol levels; they further reported that malaria parasite density was significantly and inversely correlated with plasma retinol, indicating a specific effect of this infection on vitamin A status. Thurnham and Singkamani (1991) also reported a significant negative association between plasma retinol and malaria in a case–control study in Thailand. These authors suggested that increased plasma retinol binding to retinol-binding protein and transthyretin causes increased availability of the vitamin to the tissues, thereby decreasing plasma retinol, while body stores might still be adequate. Thus, plasma retinol may be a doubtful measure of retinol status during malarial infections. In a later cross-sectional study in India, this was supported by the observation that levels of retinol-binding protein, which are influenced by the acute phase response, explain 95% of the variation in plasma retinol in malaria patients (Das *et al.*, 1996). At least seven other cross-sectional or case–control studies have consistently found that plasma levels of retinol were decreased in malaria cases compared with matched healthy controls. In the randomized placebo-controlled study of the effect of retinol on mortality in 21 906 children from Ghana (see above), there was no difference in the malaria mortality rate or fever incidence rate and no correlation between plasma retinol at baseline and subsequent malaria parasitaemia in the placebo group (Binka *et al.*, 1995).

A range of cross-sectional studies and case–control studies have also found an association between infection with various intestinal helminths and low plasma retinol levels. The observation that ascariasis does not influence vitamin A absorption (Ahmed *et al.*, 1993) while treatment with mebendazole may increase plasma retinol levels (Curtale *et al.*, 1994) indicates that helminth infestation *per se* may change retinol distribution without affecting body stores of the vitamin.

An inverse association between infection with human immunodeficiency virus (HIV) and plasma retinol level has been found in several studies. However, a prospective study in a highly endemic area for heterosexual HIV transmission in Rwanda gave no indication of a correlation between baseline retinol levels and the subsequent risk for seroconversion in a group of 119 sexually active women followed over a 24-month period (Moore *et al.*, 1993). In a prospective study of 21 HIV-infected children and 21 controls from France, plasma retinol levels decreased with severity of the disease (Periquet *et al.*, 1995). It has been postulated that HIV infection decreases plasma retinol levels by decreasing the formation and release of retinol-binding protein from the liver, so

that body stores of retinol might be adequate while the plasma level remains low (Rosales & Ross, 1996).

In a study of 338 HIV-positive mothers in Malawi, serum retinol concentrations were inversely correlated with risk of HIV transmission to children who survived for more than 12 months ($p < 0.0001$) (Semba *et al.*, 1994). Since serum retinol may reflect severity of disease in the mothers, the result may be a consequence of this association rather than an effect of retinol *per se*. [The Working Group noted that at least four randomized trials are in progress to test vitamin A supplementation in HIV-positive pregnant women in order to resolve this issue.]

The impact of retinol on respiratory infections has been addressed in several studies, with inconsistent outcomes. In a placebo-controlled study of infant morbidity, the impact of 209 μmol vitamin A given immediately after delivery to a group of 50 low-income mothers from Bangladesh was investigated (Roy *et al.*, 1997). A significant decrease was observed in the duration of respiratory tract infections (3.1 days); 95% CI, 2.7–3.5 versus 3.7; 95% CI, 3.3–4.2; $p < 0.03$) and of the mean incidence of febrile illness (0.1; 95% CI, 0.1–0.1 versus 0.3; 95% CI, 0.3–0.3; $p < 0.002$) in breast-fed infants of vitamin A-supplemented mothers. In a randomized controlled trial of 147 pre-school children with frequent respiratory tract infections, supplementation with 450 μg/day of retinol decreased significantly the number of episodes of respiratory symptoms over a period of 11 months (Pinnock *et al.*, 1986). The effect of retinol on established respiratory infection has also been addressed in a few studies. In two multicentre randomized, placebo-controlled studies of 239 and 180 children, respectively, with respiratory syncytial virus infection, there was no evidence of a beneficial effect of vitamin A therapy (Bresee *et al.*, 1996; Dowell *et al.*, 1996). In a randomized study of 24 hospitalized patients with pneumonia in São Paulo, Brazil, who were all immediately treated with penicillin, intervention on day 1 with 200 000 IU of vitamin A did not affect plasma vitamin A on day seven, when all patients were improving. The authors state that these results support the hypothesis that low plasma levels of vitamin A during the acute phase of infection can be independent of vitamin A status (Velasquez Melendez *et al.*, 1995).

Coutsoudis *et al.* (1991) found a significant difference in plasma vitamin A levels in children with measles depending on supplementation with retinol. Such supplementation appears to carry clinical benefit in certain populations. In a randomized placebo-controlled trial of vitamin A treatment on morbidity in children hospitalized with measles in South Africa, Hussey and Klein (1990) observed a significant beneficial action of vitamin A. Similar results were reported previously in a study in Tanzania (Barclay *et al.*, 1987).

5.3 Effects on vascular or heart disease

In a prospective study of antioxidant vitamin intake and coronary heart disease (CHD) among 87 245 nurses (all females) in the United States, the risk of CHD was 0.70 (95% CI, 0.5–0.9) in the highest versus the lowest intake groups for total vitamin A (Manson *et al.*, 1991). [The Working Group noted that these results have been published only in an abstract.] In another prospective study of 34 486 postmenopausal women in Iowa, United States, followed for eight years, there was no apparent association between risk for CHD and vitamin A intake from diet or self-administered supplements (Kushi *et al.*, 1996).

The Beta-Carotene and Retinol Efficacy Trial (CARET) was a double-blind, randomized, placebo-controlled primary prevention trial (see Section 4.1.2.1(*b*)), in which retinol (25 000 IU/day) and β-carotene (30 mg/day) or placebo was administered for an average of four years to a group of 18 314 current or former smokers, or asbestos workers, aged 45–69 years. The study was designed primarily as a cancer prevention study, but several endpoints were monitored, including various forms of cardiovascular disease and total deaths. There was no improvement in any of these conditions in the intervention group as compared to the placebo group (Omenn *et al.*, 1996b). The intervention group experienced a 17% higher mortality rate (95% CI, 1.0–1.3; $p < 0.05$) and a

26% higher rate of cardiovascular disease deaths (95% CI, 1.0–1.6). The authors concluded that the combination of β-carotene with retinol had no benefit on health within the four-year follow-up period and may have had an adverse effect on cardiovascular disease and overall mortality.

In an intervention trial in Linxian county, China, described fully in Section 4.1.2.1(*a*), subjects receiving retinyl acetate (10 000 IU) with β-carotene showed a significant reduction in deaths from cerebrovascular disease among males (RR, 0.45), but not among females (RR, 0.90).

Administration of retinol (60 000 IU/day) in combination with 300 mg nicotinic acid and 140 mg tocopherol daily decreased LDL cholesterol and marginally increased HDL cholesterol in twelve patients suffering from hypercholesterolaemia (Odetti *et al.*, 1984). A positive correlation between plasma HDL cholesterol and intake of antioxidant vitamins, including intake of vitamin A, has also been observed in subgroups of white women and non-smoking black men in the CARDIA (Coronary Artery Risk Development in Young Adults) study cohort, which comprises 2193 men and 2654 women, 49% blacks and 51% whites, aged 18–30 years, living in the United States (Slattery *et al.*, 1995). Moreover, a single oral supplementation with 20 000 IU of vitamin A increased the *in vitro* oxidation resistance of LDL isolated before and eight hours after supplementation (Livrea *et al.*, 1995).

In a cross-sectional study of 10 359 randomly selected Scottish men and women aged 40–59 years, the risk for subsequent CHD among men was lower in the highest quintiles of intake of total vitamin A, fibre, β-carotene and vitamins C and E, whereas no such relationship was observed for retinol. No significant relationship between total vitamin A or retinol intake and CHD was observed in women (Bolton Smith *et al.*, 1992). In a cross-sectional study of the relationship between coronary artery disease and plasma levels of several vitamins in 72 elderly subjects, vitamin A and E levels were independently and inversely related to the risk of the disease after adjustment for confounders (Singh *et al.*, 1995).

5.4 Other preventive actions

5.4.1 Degenerative conditions of ageing

Some recent reviews have considered the evidence for beneficial antioxidant effects of retinoids in preventive geriatrics (Ward, 1994, 1996). Although there is some theoretical and laboratory evidence that retinol might be protective against degenerative changes in the skin, eye and immune system due to antioxidant action, relevant clinical and epidemiological evidence is scarce.

5.4.2 Arthritis

In a prospective case–control study, Comstock *et al.* (1997) investigated the association between serum levels of antioxidant vitamins and the risk for rheumatoid arthritis and lupus erythematosus. Retinol levels were lower in the serum from patients who subsequently developed either of these conditions. Low plasma levels of vitamin A have also been found in patients with rheumatoid arthritis (Honkanen *et al.*, 1989) and in patients with juvenile rheumatoid arthritis (Bacon *et al.*, 1990) as compared with unmatched controls. Serum levels of retinol were not decreased in cases with spondylitis or ankylosing hyperostosis (Mezes *et al.*, 1986). Finally, it has been reported that in patients with Sjögren's syndrome, supplementation with 100 000 IU of vitamin A daily for 14 days improved immunological performance (Szöcsik *et al.*, 1988).

5.4.3 Other protective antioxidant effects

A mixture of antioxidant vitamins (α-tocopherol, ascorbic acid, vitamin B complex and retinol) given intravenously before operation prevented oedema and lipoperoxidation due to reperfusion damage after revascularization operations of the leg in 24 patients as compared to 27 control patients (Rabl *et al.*, 1995). There was no indication however, that this effect was specifically related to retinol.

5.4.4 Lung function

In a study of 816 current and former asbestos-exposed workers who formed part of the pilot group in the CARET study (see above), lung function determined at baseline was compared with serum retinol levels. There was a

significant increase of 70 mL in forced expiratory volume (FEV_1) between the 25th to the 75th percentiles for serum retinol level.