# Antioxidants in Health and Disease: The Big Picture

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**Abstract**

*In December 1993, four reports appeared describing the ecology of macular degeneration (MD).[1-4] It was generally agreed that the environmental contribution includes sunlight. It was suggested that the antioxidants serve to counter the oxidative damage. In any case, the articles prompted a letter to the editor entitled, "Now That We Have All The Pieces... Why Is There Still A Puzzle? ".[5] This was intended to indicate that we still have very little opportunity to slow and/or stop the degenerative process. We have even less knowledge about how to reverse and/or prevent MD.*

*This report is intended to cast additional light on the subject. It is suggested that, viewed in the bigger picture, the total body concept, significant changes in macular degeneration and other diseases may occur when larger-than-recommended amounts of the antioxidants are supplied. Additionally, it is proposed that the therapy be instituted for longer periods of time and begun earlier in life. It is hoped that this report will continue more action in the pursuit of this approach to macular degeneration.*

## Introduction

The literature is replete with information which suggests that a common denominator in the aging process and in the major diseases associated with aging is oxidative damage. This has led to an interest in the use of antioxidants in the prevention and treatment of such problems. There are hundreds, if not thousands, of articles on this subject. Some are retrospective; other prospective. They deal with large and small samples of short and long duration. They range from the womb to the tomb. Most of them are of an epidemiologic (correlational) nature. However, many are concerned with intervention and possibly provide causal data.

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This report will outline evidence to show that the antioxidants are necessary, singly, in combinations, in larger amounts than generally held, and must be started much earlier in life. Hence, we will attempt to emphasize the relationship of antioxidants to common disorders such as heart disease, cancer, diabetes, arthritis, cataracts, and macular degeneration as well as other syndromes through an examination of 40 representative studies in the English language literature.

## Vitamin A Studies

Included (Table 1) are five representative studies of vitamin A consumption in health and disease.[6-10] According to the Subcommittee on Foods and Nutrition of the National Research Council, the daily recommended requirements (RDA) for vitamin A are 5,000 and 4,000 IU respectively for men and women.[11] It is clear from Table 1 that much larger amounts than proposed for healthy people in the RDA are needed. Additionally, the evidence from these studies suggest that there were no side effects.

It is generally recognized that vitamin A blood levels below 10 mcg% are considered evidence of obvious deficiency.[12] Olson contends that the normal range is 20 to 50 mcg% and therefore anything above 50 is high.

Table 2 summarizes the studies on vitamin A in the blood in health and sickness. [13-17] You will note that the reports shown suggest that what Olson call high levels are probably the desired amounts.

## Vitamin C Studies

According to the Recommended Dietary Allowances, 60 mg of vitamin C is the suggested normal requirement." Table 3 features studies which underscore the desirability of larger-than-recommended , amounts.[18-22] It will be noted that amounts as large as three grams per dose provide remarkable consequences.

Back in the '40s, the Interdepartmental Committee on Nutrition for National Defense (ICNND) began to set the standards for optimal plasma vitamin C. Originally, acceptability was anything above 0.1 mg%. Through the '40s, the figures were changed to 0.2 and then 0.4 mg%. Most of the literature today considers 0.4 mg% as being a satisfactory blood vitamin C level. In this connection, Block points out that 15% of white men, 65-74 years of age, in the U.S. today have blood ascorbate levels below 0.4 mg%.[23] Chandra views 0.5 to 2.0 mg% as the acceptable range.[24] It is clear from Table 4 that the best clinical results parallel plasma levels above 1.0 mg%.[17,25-28]

**Vitamin E Studies**

According to the RDA, 30 mg of vitamin E or 10 mg of alpha tocopherol is considered the recommendation for healthy man.[11] It will be noted (Table 5) that amounts ranging from 400 to 3200 mgs contribute to the solution of many classical problems.[29-33]

There is not much in the literature regarding the optimal blood vitamin E levels. Machlin, in his book,[34] indicates that anything less than 0.7 mg% is deficient, levels between 0.7 and 0.9 are low, and values above 0.9 mg% are acceptable. Simonoff adds the fact that the blood levels of vitamin E are different in the sexes and at different ages.[35] For example, in the young adult, the values should be 1.6 to 1.9 mg% and decrease with age to 0.9 to 1.1 mg% in the elderly. In the light of these so-called norms, it is interesting (Table 6) that salutory effects seem to parallel higher blood vitamin E levels.[14,36-39]

**Other Antioxidants**

While vitamins A, C, and E have been recognized for a long time for their antioxidant properties, there are others such as zinc, selenium, and bioflavonoids which directly or indirectly serve as free radical scavengers. Perhaps the one receiving the most attention at the moment is the Carotenoids and particularly beta carotene. Since beta carotene serves as a provitamin A, there are suggestions as to its daily requirement.[11] However, beta carotene also serves an independent function as an antioxidant. The requirement in this regard is not very clear.

Table 7 outlines the relationship of dietary beta carotene to some of our major problems.[40-44] There seems to be no question but that beta carotene in larger-than-generally-recommended amounts exert salutory effects.

In line with our earlier format, Table 8 outlines the blood carotene levels.[14,45-48] In general, the levels in health are considerably larger than those with illness.

**The Antioxidant Index**

Perhaps more importantly is the observation that the relationship between various antioxidants in health and disease are sharpened when they are viewed as an antioxidant index. For example, macular degeneration,[26] colorectal adenomas,[49] rheumatoid arthritis,[50] cancer,[51] and cardiovascular disease,[52] become even more meaningful when viewed in terms of conditions of antioxidants rather than single ones.

**Comments**

We have been trying to answer the question of the role of antioxidants in the aging process and in age-related diseases. We think that we have some of the answers. It would seem, from what has transpired, that the antioxidants are important in the prevention and treatment of these problems. However, there are still unanswered questions. We still do not know all of the antioxidants. We are still not sure of the dosages except that they are larger than usually recommended. We have little information about the amounts for different diseases. For example, are the dosages larger for macular degeneration than heart disease? Or, are the amounts more a function of the oxidative damage? And, perhaps more importantly, we do not have the time frame period.

Since the disturbances associated with aging and these age-related diseases are characterized by a long incubation period and an insidious clinical course, the question of when one should institute an antioxidant program is still unresolved. The one thing we know for sure is starting when the disease appears is too late.

**Summary and Conclusions**

In the final analysis, how we fare is a function of two sets of interdependent fac-

tors. On the one hand, we are at the mercy of numerous environmental threats, such as physical, chemical, microbial, thermic, actinic, and psychologic. For macular degeneration, the dominant one is solar radiation; for lung cancer, it is tobacco consumption. However, how we fare is also a function of how well we tolerate these environmental challenges. These protective systems are collectively referred to as resistance/susceptibility, constitution, predisposition, immunocompetence, homeostasis and/or harmony. The antioxidants serve as an important ingredient in building resistance and reducing susceptibility and largely because of its free radical scavenging action. However, how much, when and for how long are still the burning questions. At the moment, in the light of these 40 representative studies, macular degeneration and cataracts enjoy positions like heart disease and cancer.

**Table 1: Dietary Vitamin A Levels**

***Reference # 6/ Precancer***

In a study of oral leukoplakia, patients were given 200,000 IU of vitamin A per week for six months versus placebo capsules. Fifty-seven per cent of vitamin A supplemented patients had complete remission and, during that time, no new lesions appeared.

***#7/HIV***

A study was done with 25 HIV patients with CD4+ T cell counts less than 800. Thirty-two per cent of the subjects had retinol levels less than 30 mcg%. Subjects taking a daily multivitamin containing modest amounts of vitamin A (1500 - 2100 mcg) had higher serum retinol levels than those taking no supplements (72 versus 42 mcg%). These observations suggest that even modest doses of vitamin A can have significant impact on serum retinol levels in advanced HIV patients.

***#8/ Cancer***

A case control study conducted among a cohort of chemical manufacturing employees provided an opportunity to test the hypothesis that lung cancer risk is inversely related to dietary intake of vitamin A. Subjects in the lowest tercile of vitamin A intake (less than 62,000 IU/week) had approximately twice the risk of lung cancer as those in the highest (greater than 100,000 IU/ week).

***#9/Respiratory Tract Infections***

Preschool-age children (157) with a history of frequent respiratory illness were randomized into vitamin A supplemented (450 mcg/day) and placebo groups. Respiratory symptoms were recorded on a daily basis over a period of 11 months. The children who received the supplement experienced 19% fewer episodes of respiratory symptomatology than their placebo counterparts.

***#10/ Mortality***

Mortality of Sumatran children randomized to receive a 200,000 IU vitamin A capsule (n=9776) was compared with those who did not (n=2447). During the four months after completion of the first distribution, mortality among the recipients was 75 per cent less than the nonrecipients. One capsule every six months may provide adequate protection for the vast majority of children.

**Table 2: Blood Vitamin A Levels**

***Reference # 13/ Measles***

In a study of children in Long Beach, California, the blood levels in youngsters with measles was 24 mcg%; in those with nonmeasles 26 mcg%; and in the well kids 40 mcg%.

***#14/Alzheimer's Disease***

Elderly people with Alzheimer's Disease, post-infarct-dementia and controls were examined. The average vitamin A levels were 45 mcg% in Alzheimer's Disease compared to an average 61 mcg% in the control group.

***#15/ Cancer***

The vitamin A blood levels of patients with pulmonary cancer, non-cancer pulmonary disease, and controls were compared. The levels were 45.6 mcg% (range 20.2 to 79.5) for the pulmonary cancer subjects; 64.3 mcg% (range 43.6 to 80.8) for the patients with noncancer pulmonary disease; and 68.4 mcg% (range 52.6 to 101.2) in the controls.

***#16/ Bronchopulmonary Disease***

This study showed that low vitamin A levels (less than 10 mcg%) observed in infants with bronchopulmonary dysplasia (BPD), and implies that therapeutic administration of vitamin A may help prevent and treat BPD.

***#17/ Cardiovascular Disease***

There is data from the cross-cultural European comparisons of the Edinburgh Aging Control Study and of the Basel Prospective Study. They show, for the first time with fair probability, that vitamin A concentrations needed to decrease ischemic heart disease risk are 63 to 80 mcg%.

**Table 3: Dietary Vitamin C Levels**

***Reference #18/Infertility***

One gram of ascorbic acid per day for 60 days was provided to 20 clearly-diagnosed infertile, but otherwise healthy, men. A separate control group of 20 men were placebo-supplemented. At the end of these two months, conception occurred unanimously only in the vitamin C supplemented couples!

***#19/Diabetes***

A study of the small blood vessels of the skin and retina was carried out in 24 normal subjects and 12 diabetics. The experiment revealed very clearly that the capillary strength of both the eye and skin of all diabetics improved during the vitamin C treatment (one gram/day) and worsened when it was discontinued.

***#20/ Mental Illness***

The manic/depressive state was assessed in 24 subjects who completed two generally accepted psychometric tests. Each patient was provided with either a three gram ascorbic acid effervescent tablet or a placebo. In the vitamin C treated group, the severity of the bipolar state was reduced within the first hour and then declined even more rapidly between the second and fourth hours. No change occurred in the placebo subset.

***#21/ Life Expectancy***

In a reexamination of a large federal government study, it was discovered that those men who consumed 300 to 400 mgs of vitamin C daily compared with those who consumed less than 50 mgs showed an overall mortality reduction of 42% principally due to a decline in heart disease and cancer. This translates into living approximately six years longer!

***#22/ Cardiovascular Disease***

A 1000 mg ascorbic acid tablet or a placebo was supplemented daily to 20 adults for two six-week periods in a randomized, crossover design. Under these conditions, vitamin C supplementation reduced the systolic pressure.

**Table 4: Blood Vitamin C Levels**

***Reference #25/ Periodontal Disease***

In a study of 24 adult volunteers with initially low and partially even deficient plasma vitamin C values, the hydroxyproline and proline content was measured before and after supplementation. There was a statistically significant rise but not before the plasma ascorbate level was above 0.9 mg%. The optimal plasma vitamin C level which was associated with the highest hydroxyproline and proline content in periodontal tissue ranged between 1.0 and 1.3 mg%.

***#17/ Heart Disease***

The most recent work on risk factors in ischemic heart disease (IHD) is available from several cross-cultural epidemiologic studies. They all suggest, for the first time with fair probability, that protection against IHD is paralleled by vitamin C levels in the range of 0.7 to 0.9 mg%.

***#26/ Macular Degeneration***

From the Eye Disease Case Control Study Group, there is evidence that blood levels of vitamin C in the 0.7 to 1.6 mg% range have a risk of one third to one half that in blood levels below 0.7 mg% for macular degeneration.

***#2 7/ Hypertension***

In a study of 685 patients without known hypertension, it was discovered that the higher the plasma vitamin C level, the lower the systolic and diastolic pressure. Specifically, with plasma ascorbic acid. (PAA) of 0.7 mg%, the blood pressure was 147/83 mm Hg; with PAA of 1.4 mg%, the pressure was 139/78 mm Hg.

***#28/ Cataracts***

*A* classification was designed of three blood ascorbate levels; less than 0.7 mg%, greater than 1.6 mg%, and a group with plasma levels at intermediate range. Persons with the lowest ascorbate intake status had 11-fold the risk of developing cataracts in the posterior region of the lens as individuals with the highest ascorbate levels.

**Table 5: Dietary Vitamin E Levels**

***Reference #29/ Cardiovascular Disease***

One of the major signs of peripheral arterial disease (PAD) is intermittent claudication. In a double-blind study, 1600 mgs of alpha tocopherol a day significantly reduced (66%) this important sign of cardiovascular disease.

***#30/ Parkinson's Disease***

*A* comparison was made of the clinical picture of Parkinson's Disease as measured by a Unified Parkinson's Disease Scale, in patients taking vitamin E in dosages from 400 to 3200 IU per day versus those not taking vitamin E. The overall and individual performance, mentation, activities of daily living, motor examination, and complications of daily living improved only in the supplemented group.

***#31/ Rheumatoid Arthritis***

The use of 1200 mg per day of vitamin E was studied in rheumatoid arthritis patients in Austria. The evidence suggests an inverse relationship between the consumption of vitamin E and a reduction in pain and stiffness.

***#32/ Cataracts***

*A* case control group of 175 cataract patients, 55 years of age or older, were matched with a like number of cataract-free subjects. The incidence of cataracts was shown to be half in those consuming more than 400 IU of vitamin E per day.

***#33/Immune Response***

The effect of daily vitamin E supplementation (800 IU alpha tocopherol for 30 days) on immune responses of 32 healthy subjects (60+ years old) was examined in a placebo-controlled, double-blind trial in a metabolic research unit. The data suggest that vitamin E supplementation improves immune responsiveness in healthy elderly.

**Table 6: Blood Vitamin E Levels**

***Reference #36/ Immune Response***

In a metabolic unit, using a double blind protocol, immune response was studied in a group receiving vitamin E (800mg per day) versus placebo. The increased immunocompetence was matched by blood vitamin E levels which jumped from 1.1 to 3.1 mg%. No such change in blood vitamin E occurred in the control group (1.1 to 1.0 mg%).

***#14/Alzheimer's Disease***

*A* comparison of vitamin E blood levels in Alzheimer's Disease (0.8 mg%), infarct-dementia (0.7 mg%) and in a group of controls (1.3 mg%) indicates that the vitamin E levels in the healthy subjects are approximately double that in the sick people.

***#3 7/ Cataracts***

In the Baltimore Longitudinal Study on Aging, using a case control design, the prediction of cataracts correlated with serum vitamin E. Specifically, those with the lowest blood levels (0.8 mg%) had an odds ratio of almost double those in the upper terciles (1.3 mg%).

***#38/ Macular Degeneration***

In the Baltimore Longitudinal Study, it was shown that those with macular degeneration (MD) have alpha tocopherol levels of 0.8 versus 1.3 mg% in the quartile free of MD. Hence, macular degeneration occurs twice as often in patients with low levels.

***#39/Diabetes***

Blood levels following supplementation of 2000 IU of vitamin E daily for two weeks was studied. The average serum tocopherol increased from 1.48 to 5.06 mg/g. This is the first time levels over 5 mg/g in the blood have been reported.

**Table 7: Dietary Beta Carotene Levels**

***Reference #40/ Cardiovascular Disease***

In the Nurses' Health Study in which a cohort of 121,000 US female nurses ages 30-55 were followed, those who consumed more than 15-20 mg/day of beta carotene had 40% lower risk of stroke and 22%) lower risk of

heart attack, compared to women who reported eating less than 6 mg/day.

***#41/ Cancer***

At the moment, this is the largest study of dietary factors and lung cancer in nonsmokers. The evidence suggests that dietary beta carotene and raw fruits and vegetables reduce the risk of lung cancer in nonsmoking men and women.

***#42/ Immune Response***

Immune system response to short-term, high-dose beta carotene supplementation was examined. Supplements of 180 mg of beta carotene per day for two weeks increased the number of T4 lymphocytes (helper cells) and did not effect the T8 lymphocytes (suppressor cells).

***#43/ Precancer***

In a study of 24 people with oral leukoplakia, given 30 mg/day of beta carotene for 3 to 6 months, there was a 71% response rate. Of particular importance was the fact that no clinically significant toxicity was observed during this trial that could be attributable to beta carotene.

***#44/ Mortality***

A study was conducted regarding the association between consumption of vegetables high in beta carotene and cardiovascular mortality in a prospective cohort of 1299 elderly Massachusetts residents. Those consuming the greatest amount (in the upper quartile) of beta carotene rich foods had one half the risk of cardiovascular mortality as those in the lowest quartile.

**Table 8: Blood Carotenoid Levels**

***Reference #14/Alzheimer's Disease***

The blood carotene levels were 7 to 23 mcg% in Alzheimer's Disease; 7 to 16mcg% in multi-infarct dementia patients versus 7 to 82 mcg% in controls.

***#45/ Precancer***

In oral and pharyngeal cancer, the blood carotene levels were 39.5 in cases versus 61.5 mcg% in control patients.

***#46/ Measles***

Beta carotene levels were 35.0 mcg% in children with measles and kerotomalacia versus 39.0 mcg% in kids with measles without kerotomalacia as compared with 64.0 mcg% in health controls.

***#47/Macular Degeneration***

The Eye Disease Case Control Study Group discovered that the chances of having macular degeneration is reduced about half in those demonstrating the larger amounts of Carotenoids in the blood (greater than 69 mcg%).

***#48/ Cardiovascular Disease***

A 12-year follow-up of cardiovascular mortality in the Basel Prospective Study revealed a significantly increased relative risk of ischemic heart disease and stroke of a magnitude of two-fold at initially low plasma levels of carotene (less than 12 mcg%) independent of the classical cardiovascular risk factors.

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