Journal of the American Optometric Association 67: #1, 50-57, January 1996.

Antioxidants in health and disease

E. Cheraskin, M.D., D.M.D.

ABSTRACT

BACKGROUND

Although numerous studies have been published about the probable causes of age-related macular degeneration, arresting or preventing the disease continues to be an elusive goal.

METHODS

The professional literature is reviewed to provide an overview of the relationship of the antioxidants to disorders such as heart disease, cancer, diabetes, arthritis, cataracts and macular degeneration.

RESULTS

Diseases associated with aging appear to have a common denominator: oxidative damage. Antioxidants have been extensively studied to determine if they can prevent or successfully treat these diseases.

CONCLUSIONS

Larger-than-recommended amounts of antioxidants need to be used earlier in life, for longer periods of time, to determine their effectiveness in arresting or preventing diseases of aging.

KEY WORDS

antioxidants, age-related macular degeneration, vitamins

Cheraskin E. Antioxidants in health and disease. J Am Optom Assoc 1996; 67:50-7.

In December 1993, four reports appeared in this journal describing the etiology of age-related macular degeneration (ARMD).[1-4] It was generally agreed that the environmental contribution includes sunlight. It was suggested that the antioxidants serve to counter the oxidative damage. Despite this information, it was apparent that practitioners still have very little opportunity to slow or stop the degenerative process and even less knowledge about how to reverse or prevent ARMD.

This report is intended to cast additional light on the subject. It is suggested that, viewed in 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 stimulate more activity in the pursuit of this approach to macular degeneration.

The literature is replete with information that suggests that a common denominator in the aging process and in the major diseases associated with aging is oxidative damage. This finding 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; others are 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.

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, this discussion will attempt to emphasize the relationship of antioxidants to common disorders such as heart disease, cancer, diabetes, arthritis, age-related cataracts, and age-related macular degeneration, as well as other syndromes, through an examination of 40 representative studies in the English language literature.

Vitamin A studies

Included in Table 1 are five representative studies of vitamin A consumption in health and disease.[5-9] 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.[10] 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 suggests that there were no side effects.

Table 2 summarizes several studies on vitamin A in the blood in health and sickness.[12-16] It should be noted that the reports shown suggests that what Olson calls 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.[10] Table 3 features studies which underscore the desirability of larger-than-recommended amounts.[17-21] It will be noted that amounts as large as three grams per dose provide remarkable consequences.

Dietary vitamin A levels

precancer[5]

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 percent of vitamin A supplemented patients had complete remission and, during that time, no new lesions appeared.

HIV[6]

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

cancer[7]

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).

respiratory tract infections[8]

Preschool-age children (n=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 percent fewer episodes of respiratory symptomatology than their placebo counterparts.

mortality[9]

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 percent less than the nonrecipients. One capsule every six months may provide adequate protection for the vast majority of children.

Table 1

It is generally recognized that vitamin A blood levels below 10 mcg% are considered evidence of obvious deficiency.[11] Olson contends that the normal range is 20 to 50 mcg% and that therefore a blood level above 50 is high.

Back in the 1940s, 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

Blood vitamin A levels

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%.

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.

The vitamin A blood levels of patients with pulmonary cancer, noncancer pulmonary disease, and controls were compared. The levels were 45.6 mcg% (range 20.3 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.

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

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

Table 2

Dietary vitamin C levels

infertility[17]

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.

diabetes[18]

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

mental illness[19]

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.

life expectancy[20]

In a reexamination of a large federal government study, it was discovered that those men who consumed 20 to 400 mgs of vitamin C daily compared with those who consumed less than 50 mgs showed an overall mortality reduction of 42 percent, principally due to a decline in heart disease and cancer. This result translates into living approximately six years longer.

cardiovascular disease[21]

A 1000 mg ascorbic acid tablet or a placebo was supplied 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 3

Blood vitamin C levels

periodontal disease[24]

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 from 1.0 to 1.3 mg%.

heart disease[16]

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%.

macular degeneration[25]

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.

hypertension[26]

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 mmHg; with PAA of 1.4 mg%, the pressure was 139/78 mmHg.

cataracts[27]

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 4

Dietary vitamin E levels

cardiovascular disease[28]

One of the major signs of peripheral arterial disease is intermittent claudication. In a double-blind study, 160 mgs of alpha tocopherol a day significantly reduced (66 percent) this important sign of vascular disease.

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. The overall and individual performance, mentation, activities of daily living, motor examination, and complications of daily living improved only in the supplemented group.

rheumatoid arthritis[29]

The use of 1200 mg/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.

cataracts[21]

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.

immune response[31]

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 persons.

Table 5

Blood vitamin E levels

immune response[34]

In a metabolic unit, using a double-blind protocol, immune response was studied in a group receiving vitamin E (800 mg/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%).

Alzheimer's disease[13]

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%) indicated that the vitamin E levels in the healthy subjects was approximately double that in the sick people.

cataracts[35]

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%).

macular degeneration[36]

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

diabetes[37]

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

Table 6

Dietary beta carotene levels

cardiovascular disease[38]

In the Nurses' Health Study, in which a cohort of 121,000 U.S. female nurses aged 30 to 55 were followed, those who consumed more than 15 to 20 mg/day of beta carotene had 40 percent lower risk of stroke and 22 percent lower risk of heart attack, compared to women who reported eating less than 6 mg/day.

cancer[39]

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.

immune response[40]

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 affect T8 lymphocytes (suppressor cells).

precancer[41]

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 percent 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.

mortality[42]

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 compared to those in the lowest quartile.

Table 7

Blood carotenoid levels

Alzheimer's disease[13]

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

precancer[43]

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

measles[44]

Beta carotene levels were 35.0 mcg% in children with measles and keratomalacia, as compared to 39.0 mcg% in children with measles without keratomalacia and to 64.0 mcg% in healthy controls.

macular degeneration[45]

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%).

cardiovascular disease[46]

A 12-year follow-up of cardiovascular mortality in the Basel Prospective Study revealed a significantly increased relative risk to 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.

Table 8

1940s, the figures were changed to 0.2 and then to 0.4 mg%. Most of the literature today considers 0.4 mg% a satisfactory blood vitamin C level. In this connection, Block points out that 15 percent of white men, 65 to 74 years of age, in the U.S. today have blood ascorbate levels below 0.4 mg%.[22] Chandra views 0.5 to 2.0 mg% as the acceptable range.[23] It is clear from Table 4 that the best clinical results parallel plasma levels above 1.0 mg%.[16,24-27]

Vitamin E studies

According to the RDA, 20 mg of vitamin E or 10 mg of alpha tocopherol is considered the recommendation for healthy men.[10] It will be noted (Table 5) that amounts ranging from 400 to 3200 mgs contribute to the solution of many classical problems.[28-31]

There is not much in the literature regarding the optimal blood vitamin E levels. Machlin, in his book,[32] indicates that anything less than 0.7 mg% is deficient, levels between 0.7 or 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.[33] 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 salutary effects seem to parallel higher blood vitamin E levels.[13,34-37]

Other antioxidants

While vitamins A, C, and E have been recognized for a long time for their antioxidant properties, there are other antioxidants 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, particularly beta carotene. Since beta carotene serves as a provitamin A, there are suggestions as to its daily requirement.[10] 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 major health problems.[38-42] There seems to be no question but that beta carotene in larger-than generally recommended amounts exert salutary effects.

Table 8 outlines the blood carotene lev-

els.[13,43-46] In general, the levels in health are considerably larger than those accompanying illness.

The antioxidant index

Perhaps more important 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,[25] colorectal adenomas,[47] rheumatoid arthritis,[48] cancer,[49] and cardiovascular disease[50] become even more meaningful when viewed in terms of combinations of antioxidants rather than single ones.

Comments

Investigators have been trying to answer the question of the role of the antioxidants in the aging process and in age-related diseases. Their results suggest that they have some of the answers. It would seem, from what has transpired, that the antioxidants are important in the prevention and treatment of numerous age-related problems. However, there are still unanswered questions. Investigators still do not know all of the antioxidants. They are still not sure of the dosages except that they are larger than usually recommended. They 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, investigators 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 that is known for sure is that starting when the disease appears is too late.

Conclusion

In the final analysis, how people fare is a function of two sets of interdependent factors. On the one hand, individuals are at the mercy of numerous environmental threats, including those that are 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 people fare is also a function of how well they tolerate these environmental challenges. These protective systems are collectively referred to as resistance/susceptibility, constitution, predisposition, immunocompetence, hemostasis and/or harmony. The antioxidants serve as an important ingredient in building resistance and reducing susceptibility, largely because of their 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—like heart disease and cancer—deserve clinical studies intended to provide clinically applicable answers to these questions.

References

1. Alexander LJ. Age-related macular degeneration: The current understanding of the status of clinicopathology, diagnosis and management. J Am Optom Assoc 1993; 64(12):822-37.

2. Richer SP. Is there a prevention and treatment strategy for macular degeneration? J Am Optom Assoc 1993; 64(12):838-50.

3. Kaminski MS, Yolton DP, Jordan WT, Yolton RL. Evaluation of dietary antioxidant levels and supplementation with ICAPS-Plus and Ocuvite. J Am Optom Assoc 1993; 64(12):862-70.

4. Van der Hagen AM, Yolton DP, Kaminski MS, Yolton RL. Free radicals and antioxidant supplementation: A review of their roles in age-related macular degeneration. J Am Optom Assoc 1993; 64(12):871-8.

5. Stitch HF, Hornsby AP, Mathew B, et al. Response to oral leukoplakias to the administration of vitamin A. Cancer Letters 1988; 40: 93-101.

6. Ward BJ, Humphrey JH, Clement L, et al. Vitamin A status in HIV infection. Nutr Res 1993; 13: 157-66.

7. Bond GG, Thompson FE, Cook RR. Dietary vitamin A and lung cancer: Results of a case-control study among chemical workers. Nutr Cancer 1987; 9(2-3):109-21.

8. Pinnock CB, Douglas RM, Badcock NR. Vitamin A status in children who are prone to respiratory tract infections. Aust Paediatr J 1986; 22(2): 95-9.

9. Tarwotjo I, Somer A, West DP Jr., et al. Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. Am J Clin Nutr 1987; 45(6):1466-71.

10. Food and Nutrition Board/Commission of Life Sciences/National Research Council. *Recommended dietary allowances, 10th ed.* Washington, D.C.: National Academy Press, 1989.

11. Olson JA. Vitamin A. In: Machlin LJ, ed. Handbook of vitamins: *Nutritional, biochemical and clinical aspects.* New York: Marcel Dekker, Inc., 1984.

12. Arrieta AC, Zaleska M, Stutman HR, Marks MI. Vitamin A levels in children with measles in Long Beach, California. J Pediatr 1992; 121(1): 75-8.

13. Zaman Z, Roche S, Fielden P, et al. Plasma concentrations of vitamins A and E and carotenoids in Alzheimer's Disease. Age Aging 1992; 21(2): 91-4.

14. Basu TK, Donaldson D, Jenner M, et al. Plasma vitamin A in patients with bronchial carcinoma. Br J Cancer 1976; 33(1):119-21.

15. Editors. Low plasma vitamin A levels in preterm neonates with bronchopulmonary dysplasia. Nutr Rev 1986; 44:202-4.

16. Gey KF, Moser UK, Jordan P, et al. Increased risk of cardiovascular disease at suboptimal plasma concentrations of essential antioxidants: an epidemiological update with special attention to carotene and vitamin C. Am J Clin Nutr 1993; 57(5 Suppl):787S-808

17. Harris WA, Harden TE, Dawson EB. Apparent effect of ascorbic acid medication on semen metal levels. Fertil Steril 1979; 32(4):455-9.

18. Cox BD, Butterfield WJ. Vitamin C supplements and diabetic cutaneous capillary fragility. Br Med J 1975; 3(5977):205-7.

19. Naylor GJ, Smith AH. Vanadium: A possible aetiological factor in manic depressive illness. Psychol Med 1981; 11(2):249-56.

20. Enstrom JE, Kanim LD, Klein MA. Vitamin C intake among a sample of the United States population. Epidemiology 1992; 3(3):194-202.

21. Osilesi O, Trout DL, Ogunwole JO, et al. Blood pressure and plasma lipids during ascorbic acid supplementation in borderline hypertensive and normotensive adults. Nutr Res 1991; 11: 405-12.

22. Block G. Vitamin C, cancer and aging. Age 1993; 16: 55-8.

23. Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet 1992; 340(8828):1124-7.

24. Buzine R, Aurer-Kozelu J, Srkak-Jorgic D, et al. Increase of gingival hydroxproline and proline by improvement of ascorbic acid status in man. Int J Vit Nutr Res 1986; 56: 367-72.

25. Eye Disease Case-Control Study Group. Antioxidant status and neovascular age-related macular degeneration. Arch Ophthalmol 1993; 111: 104-9.

26. Jacques PF. Relationship of vitamin C status to cholesterol and blood pressure. Ann N Y Acad Sci 1992; 669: 205-14.

27. Jacques PF. Effects of vitamin C on high density liproprotein cholesterol and blood pressure. Am J Coll Nutr 1992; 11(2):139-44.

28. Williams HT, Fenna D, MacBeth RA. Alpha tocopherol in the treatment of intermittent claudication. Surg Gynecol Obstet 1971; 132(4): 662-6.

29. Scherak O, Kolarz G. Vitamin E and rheumatoid arthritis. Arthritis Rheum 1991; 34(9):1205-6.

30. Robertson JM, Donner AP, Trevithick JR. Vitamin E intake and risk of cataracts in humans. Ann N Y Acad Sci 1989; 570: 372-82.

31. Meydani SN, Barklund MP, Liu S. Effect of vitamin E supplementation on immune responsiveness of healthy elderly subjects. FACEB 1989; 3: A1057.

32. Machlin LJ. Handbook of vitamins: National, biochemical and clinical aspects. New York: Marcel Dekker, Inc., 1984.

33. Simonoff M, Sergeant C, Garnier N, et al. Antioxidant status (selenium, vitamins A and E) and aging. EXS 1992; 62:368-97.

34. Meydani SN, Barklund MP, Liu S, et al. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. Am J Cln Nutr 1990; 52(3):557-63.

35. Vitale S, West S, Hallfrisch J, et al. Plasma antioxidants and risk of cortical and nuclear cataract. Epidemiology 1993: 4(3):195-203.

36. West S, Vitale S, Hallfrisch J, et al. Are antioxidants or supplements protective for age-related macular degeneration? Arch Ophthalmol 1994; 112(2):222-7.

37. Bierenbaum ML, Noonan FJ, Machlin LJ, et al. The effect of supplemental vitamin E on serum parameters in diabetics, post coronary and normal subjects. Nutr Rep Int 1985; 31: 1171-80.

38. Manson JE, Stampfer MJ, Willett WC, et al. A prospective study of antioxidant vitamins and incidence of coronary heart disease in women. Circulation 1991; 84(II): 546 (abstract).

39. Mayne ST, Janerist DT, Greenwald P, et al. Dietary beta carotene and lung cancer in U.S. nonsmokers. J Nat Cancer Inst 1984; 86: 33-8.

40. Alexander M, Newmark H, Miller RG. Oral beta-carotene can increase the number of OKT4+ cells in human blood. Immunol Lett 1985; 9: 221-4.

41. Garewal HS, Meyskens FL, Killen D, et al. Response of oral leukoplakia to beta carotene. J Clin Oncol 1990; 8(10):1715-20.

42. Gariano M, Manson JE, Branch LG, et al. Dietary beta carotene and decreased cardiovascular mortality in an elderly cohort. J Am Coll Cardiol 1992; 19: 337A.

43. Ibrahim K, Jafarey NA, Zuberi SJ. Plasma vitamin A and carotene levels in squamous cell carcinoma of oral cavity and oro-pharynx. Clin Oncol 1977; 3(2):203-7.

44. Laditan AAO, Fafunso M. Serum levels of vitamin A, beta-carotene and albumin in children with measles. East Afr Med J 1981; 58(1):51-5.

45. The Eye Disease Case Control Study Group. Risk factors of neovascular age-related macular degeneration. Arch Ophthalmol 1992; 110(12):1701-8.

46. Gey KF, Stahelin HB, Eichholzer M. Poor plasma status of carotene and vitamin C is associated with higher mortality from ischemic heart disease and stroke: Basel Prospective Study. Clin Investig 1993; 71(1):3-6.

47. Roncucci L, DiDonato P, Carati L, et al. Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. Dis Colon Rectum 1993; 36(3):27-34.

48. Heliovaara M, Knekt P, Aho K, et al. Serum antioxidants and risk of rheumatoid arthritis. Ann Rheum Dis 1994; 53(1):51-3.

49. Eichholzer M, Stahelin HB, Gey KF. Inverse correlation between essential antioxidants in plasma and subsequent risk to develop cancer, ischemic heart disease and stroke respectively: 12-year follow-up of the Prospective Basel Study. EXS 1992; 62:398-410.

50. Manson JE, Stampfer MJ, Willett WC, et al. Antioxidant vitamins and secondary prevention of cardiovascular disease in high risk women. Circulation 1993; 88(I):1-70.

Submitted10/94; accepted 10/95

E. Cheraskin, M.D., D.M.D.
School of Medicine
University of Alabama at Birmingham
Birmingham, AL 35294