

SUPPORTIVE INFORMATION for Bruce N. Ames Perspective

SI-1-Vitamin and Mineral Deficiencies

Numerous studies link poor nutrition to a variety of diseases of aging, as shown in the following sampling of recent references (1-12).

SI-2-Triage Theory

Vitamin K (phylloquinone) is necessary for the function of 16 enzymes. A triage rationing process is supported by an analysis of the behavior of these enzymes under a mimic of vitamin K shortage (13). Recent studies provide additional support: a Mendelian Randomization (MR) epidemiology study showed that both all-cause and cardiovascular disease (CVD) mortality are caused by vitamin K1 inadequacy, and confirmed that the low level of the inactive form of Mgp protein, which normally prevents arterial calcification, is diagnostic for vitamin K1 deficiency (14). Increased dietary intake of vitamin K1 and menaquinone (K2=MK2) and other derivatives (such as MK7 in natto) was associated with lower all-cause cancer and CVD mortality (15). A study of 166 adolescents supports the CVD findings by showing that subclinical cardiac structure and function variables are most favorable at higher phylloquinone (vitamin K1) levels (16).

Selenium is necessary for the function of 25 enzymes. A triage-related rationing was also shown to be operating in the case of selenium (17). A 4-year Randomized Clinical Trial (RCT) (18) of selenium supplementation (200 µg/d) +CoQ10 (200mg/d) significantly reduced CVD mortality risk by more than 40%, and also significantly reduced hypertension, IHD, impaired cardiac function, and diabetes in 443 elderly people in rural Sweden (where soil is low in selenium) during a follow-up time of 12 years; improvement in CVD biomarkers, such as echocardiography and natriuretic peptide levels, was also observed.

SI-3-Survival V/M that are also Longevity V/M

Vitamin D: A meta-analysis of vitamin D versus mortality in 5 Northern European countries (n~29,000), using subjects of median age 62 years, showed that a blood level of 25(OH)D of less than 12 ng/ml was associated with maximum mortality, while levels between 30 to 40 ng/ml were associated with the lowest mortality (19). Rodent evidence also showed that mutations in the vitamin D receptor in mice resulted in premature aging (20). A meta-analysis of 32 studies (n = ~500,000) on vitamin D and all-cause mortality showed that the mortality hazard ratio between subjects with the lowest quantile (<9 ng/ml) and those with the highest (>50 ng/ml) serum levels of 25(OH)D was 1.9 (p=0.001). Levels of 25(OH)D less than or equal to 30 ng/ml were associated with significantly higher (p < .01) all-cause mortality than levels greater than 30 ng/ml (21). A 12-year German study of elderly individuals (n=9,579) in a statistically simulated intervention with vitamin D showed a large decrease in all-cause mortality and cancer (22).

A 29 year-long study of 95,000 Danes showed that a decreased plasma level of 25(OH)D was associated with early mortality and an increased risk of ischemic heart disease and myocardial infarction (23). An MR analysis of this study showed that a low 25(OH)D level was causally associated with all-cause mortality and cancer mortality

(although not with cardiovascular mortality) (24). The latter lack of effect of vitamin D on CVD was replicated in a Canadian MR study of 34,000 people of European descent (25). However, a recent study found that supplementation with high doses of vitamin D for a year significantly reduced blood pressure (26). A RCT on vitamin D3 supplementation on 70 young overweight African-Americans with vitamin D deficiency showed amelioration in arterial stiffness (27).

Deficiency of vitamin D is associated with increased risk of cancer incidence and risk of mortality, as reviewed recently (28). An estimate has been made that doubling the mean concentration of 25(OH)D in the population would reduce the mortality rate by about 20% and increase life expectancy by two years (29). Meta-analyses of the numerous vitamin D mortality studies showed a consistent correlation between increasing vitamin D levels and a decrease in cancer, CVD, and all-cause mortality (30). Another Mendelian Randomization study performed on 31,719 European women indicated that vitamin D deficiency is causally related to ovarian cancer (31).

The rate of decay of brain function in humans is faster in individuals with lower vitamin D levels (32). Executive function improvement, as measured by visual memory, was more effective with supplementation of 4,000 IU/day of vitamin D as compared to 400 IU/day (33). An inverse relationship was observed between maternal and umbilical cord blood concentrations of 25(OH)D and serotonin concentrations, leading to the proposal that vitamin D deficiency contributes to longer-term neurocognitive impairment in infants and children (34). Both of these studies are in agreement with the finding that vitamin D activates the gene for synthesizing brain serotonin which controls executive function (35). The importance of serotonin in brain executive function was also shown in a study that linked low serotonin levels to mild cognitive impairment in the brain (36).

Diabetes may also be affected by the level of vitamin D: a meta-analysis using 24 RCTs with 4,000 IU per day of vitamin D3 in 1,528 type-2 diabetics showed that vitamin D significantly reduced fasting plasma glucose, HOMA-IR, and hemoglobin A1C (37).

Magnesium: A prospective study of ~7,000 Mediterranean adults with high CVD risk and eating diets containing varying magnesium content showed that Mg intake is inversely associated with all-cause mortality; these results are consistent with previous studies, as reviewed (38). Adequate magnesium was shown to protect against colorectal adenoma in a study investigating the effect of the magnesium /calcium ratio (39); this study included an analysis of a polymorphism in a magnesium transporter which also implicated magnesium deficiency in raising colorectal cancer risk. A review of the effects of magnesium deficiency showed increased DNA damage, telomere shortening, increased ceramide level, and an association with aging, heart disease, and colorectal cancer risk (40). There is also a significant inverse association between magnesium intake (as well as potassium intake) and risk of stroke (41, 42). Magnesium is required by almost all of the ~50 DNA repair enzymes: low dietary magnesium intake was shown to be associated with poorer DNA repair capacity and increased risk of lung cancer (43). Various reviews on how to best assay for magnesium deficiency and to determine the optimum magnesium intake are available (44).

SI-4-Conditional Vitamins

Taurine: A large rodent literature on taurine is consistent with the many human studies. The essentiality of taurine was demonstrated in cats (which have unusually low

ability to synthesize taurine) (45) and mice for the embryonic/fetal development of the brain and CNS, eyes, skeletal system, muscles, and many other tissues/organs (46, 47). Taurine is present in high concentrations in rat heart. In several rat and mouse models of heart disease taurine decreases hypertension, impairment of intimal thickening, arteriosclerosis, vascular reactivity, oxidative stress, and inflammation (reviewed in (48)). It regulates the mitochondrial respiratory chain in rat heart: its deficiency impairs cardiac mitochondrial respiratory function and causes cardiac myopathy (49). In rodent models for stroke and abdominal aortic aneurism formation taurine was shown to have protective effects (50, 51).

The importance of taurine in brain function was shown in rats, where it is present at high concentrations (52). It displayed a dose-dependent protection in a rat model of brain injury (53) and protected against traumatic brain injury by increasing mitochondrial function and cerebral blood flow in rats (54).

Taurine's function as an osmolyte was shown by studying the effect of its depletion in a wide variety of species and on several organs. It participates in controlling cell volume in a variety of cells (55, 56); it modulates calcium flux, thus affecting the contractile response in heart and muscle, insulin levels, blood pressure, and membrane polarization (55); it is the most osmotically active molecule in the brain (57). Its supplementation helps reduce the risk of diseases involving defective protein-folding by acting as a stabilizing chaperone for the proper folding of proteins as they come off the endoplasmic reticulum (58-61).

Numerous studies in experimental animals have shown the importance of the ability to transport taurine, with damaging effects in several tissues if the transport system is defective: mouse brain, liver, eyes, skeletal muscles, immune cells, olfactory system, auditory system, and heart (62-68). Skeletal muscle aging is accelerated in taurine transporter knock-out mice (69).

SI-5-Putative Longevity Vitamins

a. Ergothioneine (ESH): One major function of ESH may be to reduce the level of the toxic oxidized ferryl form of heme proteins *in vivo*, such as myoglobin, not designed to function as heme peroxidases (70, 71). One of the problems in Alzheimer's disease appears to be that the amyloid- β peptide in the brain binds heme very tightly, which leads to a temporary shortage of heme; this causes complex IV in mitochondria to release hydrogen peroxide, which then converts the amyloid- β heme into a toxic ferryl heme peroxidase that damages the cell (72). ESH has been shown to be an effective inhibitor of myeloperoxidases and is more effective than glutathione and ascorbic acid (73). *In vitro*, ESH inhibits the amyloid- β heme peroxidase more effectively than any other antioxidant examined. Perhaps relevant to the primary role of ESH in reducing the level of ferryl heme is the presence of the ESH transporter gene within a cluster of genes involved in mitochondrial heme biosynthesis (74).

ESH effectively protects against copper-dependent oxidative damage to DNA and protein by forming a redox-inactive complex with Cu(I); redox-inactive copper may play a detrimental role in Alzheimer's disease (75).

b. Pyrroloquinoline quinone: Experiments in PQQ-deficient rats and mice lend additional support to the concept that PQQ is a longevity vitamin (76-81). PQQ influences the expression of many rat genes, including genes involved in metabolic stress, cell signaling, immune function, cellular transport, cellular growth, cell cycling,

extracellular matrix formation, mitochondrial functions, lipid-related and phospholipid-related functions (82). PQQ also modulates mitochondrial quantity and function (in mice) (83), and mitochondrial lipid and energy metabolism (in rats) (79). With respect to mitochondrial function, a study found that when PQQ was incorporated into mouse hepatocytes, it stimulated mitochondrial biogenesis *via* induced PGC-1 α activation (84). Mice deprived of PQQ became osteolathyrotic, which was reversed by the addition of PQQ to the diet. *In vivo*, PQQ improved glucose tolerance in type-2 diabetic mice (85). In surgically injured young rats, PQQ had an analgesic effect on neuropathic pain (86). PQQ enhanced cognitive function in rats and prevented cognitive deficit under oxidative stress (87, 88).

c. Queuine: Results from mice suggest that the intestinal-flora is capable of supplying queuine in sufficient quantities to metazoans. Animals fed a chemically defined diet that is devoid of queuine showed no change in the relative amounts of queuine-modified and unmodified tRNA (Farkas 1980). By contrast, mice maintained on a chemically-defined diet under germ-free conditions became fully depleted of queuine in all four tRNAs after one year (89). Feeding these animals purified *E. coli* tRNA showed that higher mammals can independently metabolise and recover queuine from tRNA (89).

The queuine modifications in aspartyl and tyrosyl tRNAs are then further modified with a mannose and a galactose, respectively (90), *via* a glycosyl linkage, whereas histidinyl and asparaginyl tRNA remain non-glycosylated (90). Notably, both cytosolic and mitochondrial tRNA are substrates for queuine-tRNA insertion (91, 92). Recently, a protein termed DUF2419 has been identified as a queuosine salvage enzyme in yeast which is conserved across diverse species (93). At the molecular level, queuine's position in the tRNA anticodon loop has been shown to influence the amino acid charging of the tRNA molecule (94) codon recognition on the ribosome (95) and the rate and accuracy of translation (96).

d. Carotenoids: Carotenoids are introduced into humans by way of their diet, where they perform the same antioxidant function of quenching singlet oxygen, which is generated either photochemically (in the human eye, for example, (97), or in dark reactions by the immune system in neutrophils (98-100), and in eosinophils (101).

Six carotenoids are present in the American diet accounting for 95% of the carotenoids found in human blood: lutein + zeaxanthin, α and β -carotene, lycopene, and β -cryptoxanthin (102). They are also found in the human brain (103, 104).

In support of the concept of carotenoids being longevity vitamins are several findings that they are involved in increasing long-term health. In a study of serum carotenoids in 13,000 Americans in the NHANES survey, an increase in all-cause mortality was associated with a low level of total carotenoids (α - and β -carotene, lutein and zeaxanthin, β -cryptoxanthin, and lycopene), or low lycopene alone (105). The more polar carotenoids (xanthophylls) and non-polar ones (such as lycopene) may display synergy (106-109). In addition, xanthophylls can rigidify membranes, thus protecting them by increasing the barrier to oxidation (108).

i. Lutein and Zeaxanthin are part of the antioxidant photosynthetic system of all higher plants. They are present in most common vegetables and fruits, in particularly high levels in kale, spinach, broccoli, and corn (110). Diet-derived lutein and zeaxanthin are found in the macula of the human eye and in lower concentrations in many other human tissues, particularly in the brain (111, 112). The macula also contains meso-

zeaxanthin, which is made in the eye from lutein (113) and will not be discussed here; see also (114). The key role of lutein and zeaxanthin in vision has been well reviewed recently (110, 114, 115).

Lutein and zeaxanthin help protect the retinal macula, which contains the photoreceptors that are critical for central vision (110, 111). They are taken up in high concentrations by the retina (116) and are bound by lutein- and zeaxanthin-binding proteins, thus forming the macular pigment (117-119).

Oral supplementation with lutein or zeaxanthin in humans or monkeys leads to a significantly increased macular pigment density (112, 120-123) and results in better eye function and protection. Lutein and zeaxanthin are believed to perform three main functions in eyes (which are the same they perform in plants) (111): 1) they filter out harmful wavelengths of strong blue light from the sky; 2) they have anti-singlet oxygen activity, and 3) they are inserted into membranes, preventing oxidation of omega-3 fatty acids, the most easily oxidized fatty acids (114, 124).

Long-term benefits derived from lutein and zeaxanthin include reducing the risk of age-related macular degeneration (AMD; the main cause of blindness in the elderly). Supplementation with lutein or zeaxanthin or both led to improved visual performance in patients with early AMD, including high contrast and low-contrast visual acuity, shape discrimination, glare recovery, and contrast sensitivity functions (125-127). A clinical trial in 112 patients with early AMD using various supplementation doses of lutein or lutein/zeaxanthin for 2 years resulted in increased macular pigment optical density and enhanced retinal sensitivity (128). The AREDS2 study (129) supports such conclusion, as shown by a secondary analysis of participants in the lowest quintile of dietary intake of lutein/zeaxanthin, which indicated a protective effect against progression to advanced AMD with a risk reduction of 26%, although this study is very complicated.

Some protection from cataract formation is obtained with an intake of a basal level of lutein and zeaxanthin (130) and protection is evident in other parts of the eye including the retinal pigment epithelium (131) and as also assessed by various parameters (116, 132, 133).

Lutein, the main carotenoid in the brain, appears to play a role in delaying brain aging (110, 134-137). For example, lutein levels in plasma and brain are associated with a higher volume of brain grey matter and with improved crystallized intelligence in the elderly (138). A double-blinded, randomized controlled trial showed that a lutein plus zeaxanthin supplement increased both neural processing speed and efficiency (139). Decreased processing speed is a major hallmark of cognitive decline. Lutein and zeaxanthin have also been shown to improve memory recall while using less brain power in older individuals (neural efficiency).

The following carotenoids are also important for human cardiovascular health: the polar marine xanthophyll, astaxanthin; the plant xanthophylls, lutein, zeaxanthin and β -cryptoxanthin; and the non-polar carotenoids lycopene and β -carotene (140). Lutein (but not β -carotene) supplementation resulted in a marked lowering of a risk factor for heart disease, carotid intima-media thickening (141-145).

Lutein, zeaxanthin, astaxanthin, and lycopene improve general health and healthy aging through their prevention and treatment of non-alcoholic fatty liver disease (146) and diabetic microvascular complications (147). Lutein and zeaxanthin levels are associated

with longer telomeres in humans (148) and lutein extends the lifespan of *Drosophila* and protects against oxidative stress (149).

High intake and high serum levels of dietary lutein lower the risk of various types of cancer (150).

In agreement with the above studies on the importance of lutein for health the suggestion was made that “A healthy diet should be considered to do more than prevent deficiencies, it must promote optimal health during the life course” (110).

ii). Lycopene, the precursor of several other carotenoids found in plants, also appears to be a longevity vitamin. It is a potent non-polar anti-oxidant, containing 11 conjugated trans double bonds and is one of the most efficient singlet oxygen quenchers known (151, 152). The highest levels of lycopene are found in the tomato (85% of U.S. intake) (153, 154). Dietary lycopene reaches many tissues in the human body, particularly testes, adrenals, liver, prostate, brain, breast, and colon, in all of which it may exert its protective actions (155, 156).

The beneficial effects of lycopene metabolism on diseases of aging, in particular through its antioxidant mechanisms, have been reviewed (157). Epidemiological studies show inverse correlations between high levels of dietary or serum lycopene and reduction of the risk of various cancers (158-160), such as prostate cancer where an inverse correlation between lycopene intake (or lycopene serum levels) and prostate cancer risk, and aggressiveness levels was found (although null associations were found in some other studies) (161-166). Lycopene also helped to reduce oxidative stress, metabolic syndrome, high blood pressure (167), and heart disease (168), and carotid media-thickness (145); it lowered the risk of myocardial infarction (169) and of metabolic syndrome (170); it significantly protected against oxidative stress in DNA (171).

Possible mechanisms for lycopene action in a wide variety of diseases of aging have been suggested (167, 168, 172-176).

iii). α - and β -Carotene, and β -cryptoxanthin are precursors of vitamin A (104). Diets high in α - and β -carotene are associated with lower risk of type-2 diabetes (177). Significant protection against breast cancer risk in Chinese women has been shown to be associated with consumption of α - and β -carotene, lycopene, lutein/zeaxanthin (but not of β -cryptoxanthin). This finding is consistent with previous studies (178). β -cryptoxanthin has been shown to inhibit lung cancer (179). A significant increase (5-8%) in leukocyte telomeres was seen in humans in the highest quartile consuming α - and β -carotene and β -cryptoxanthin, as compared with the lowest quartile (180). Consumption of β -carotene, and β -cryptoxanthin has also been associated with protection against hearing loss in a large (12,789 women) prospective study of hearing loss (181). A positive effect of β -carotene on cognitive function was observed, but only after prolonged treatment (12 years) (182).

iv). Astaxanthin (ASX) also is a putative longevity vitamin. It is a marine orange-red carotenoid in the xanthophyll class present in salmon, trout, red snapper, tilapia, crab, shrimp and lobster, octopus, and squid, and many other kinds of seafood and freshwater fish (183-189). It is synthesized primarily by various kinds of marine microalgae and functions to counter oxidative stress (190-193). ASX is a 4, 4' diketo zeaxanthin (109) which contains 13 conjugated double bonds. It is somewhat similar in structure to zeaxanthin (109), which contains only 11 conjugated double bonds.

ASX is absorbed into the human bloodstream and eye (194-199) with consequent improvements in visual acuity and amplitude of accommodation, and thus to healthy aging (200, 201). ASX appears to enter cells through non-specific transport systems that transport xanthophylls such as zeaxanthin and lutein, since it is similar in structure to those compounds; they might spare each other.

ASX has been shown to be a particularly strong antioxidant in studies on lipid peroxidation (109, 202). It prevented lipid peroxidation in membranes and was considerably more potent than either lutein or zeaxanthin (109, 203, 204). It quenches singlet oxygen (106, 151). It has been suggested that the alternating polar-nonpolar-polar structure of ASX, and other oxygen-containing more polar xanthophylls, allows it to span cellular and organelle membranes and thus perform better antioxidant functions against lipid peroxidation (205). The family of xanthophyll carotenoids rigidify membranes and limit O₂ penetration (108). ASX has been shown to be an effective antioxidant against damage from reactive nitrogen species (in addition to lutein and zeaxanthin), such as peroxynitrite derived from nitrogen oxide, (206, 207). It is common only in diets containing abundant marine foods, such as in the Japanese diet.

A comprehensive review of ASX action (204) concluded that it has potential health-promoting effects in the prevention and treatment of numerous diseases related to aging. A recent review of the literature (208), including 3 positive Japanese RCTs, concludes that ASX reduces cognitive and memory dysfunction with age. A review of ASX studies in humans (10 trials) and animals (12 studies) with an emphasis on cardiovascular health and disease, concluded that ASX reduced thrombosis; myocardial infarct size; oxidative damage to DNA, protein, and lipids; and blood pressure (209). See also (210). ASX significantly decreased inflammation and DNA oxidation and it enhanced the immune response in humans (211). In a study on ulcers in humans infected with *H. pylori*, ASX significantly decreased gastric inflammation (212). In human clinical trials supplementation of ASX was shown to lead to significant reductions in oxidative stress, hyperlipidemia, and levels of inflammatory markers (213).

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