PERSPECTIVE

Prolonging healthy aging: Longevity vitamins and proteins

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It is proposed that proteins/enzymes be classified into two classes according to their essentiality for immediate survival/reproduction and their function in long-term health: that is, survival proteins versus longevity proteins. As proposed by the triage theory, a modest deficiency of one of the nutrients/cofactors triggers a built-in rationing mechanism that favors the proteins needed for immediate survival and reproduction (survival proteins) while sacrificing those needed to protect against future damage (longevity proteins). Impairment of the function of longevity proteins results in an insidious acceleration of the risk of diseases associated with aging. I also propose that nutrients required for the function of longevity proteins constitute a class of vitamins that are here named "longevity vitamins." I suggest that many such nutrients play a dual role for both survival and longevity. The evidence for classifying taurine as a conditional vitamin, and the following 10 compounds as putative longevity vitamins, is reviewed: the fungal antioxidant ergothioneine; the bacterial metabolites pyrroloquinoline quinone (PQQ) and queuine; and the plant antioxidant carotenoids lutein, zeaxanthin, lycopene, α- and β-carotene, β-cryptoxanthin, and the marine carotenoid astaxanthin. Because nutrient deficiencies are highly prevalent in the United States (and elsewhere), appropriate supplementation and/or an improved diet could reduce much of the consequent risk of chronic disease and premature aging.

vitamins | essential minerals | aging | nutrition

I propose that an optimal level of many of the known 30 vitamins and essential minerals/elements (V/M), plus that of 11 new putative vitamins described herein, is necessary for promoting healthy aging. The "triage theory" (1) had previously introduced the concept that proteins/enzymes that are sacrificed on a V/M shortage are necessary for supporting long-term health. This insight is being broadened here to classify also many V/M as necessary for supporting long-term health. I present evidence that the deficiency of many V/M specifically increases the risk of future disease and shortens the lifespan. Thus, I propose that such V/M be named "longevity vitamins," and that proteins associated with them be named "longevity proteins." Prolongation of healthy aging has not been generally understood as being related to V/M levels.

Deficiencies in Vitamins and Minerals

Approximately 30 V/M are cofactors necessary for metabolism to function properly and were discovered because severe dietary deficiencies were linked to serious adverse health effects. They include vitamins A, B_1, B_2, B_6, B_{12}, biotin, C, choline, D, E, folic acid, K, niacin, pantothenate; and minerals/elements calcium, chloride, chromium, cobalt, copper, iodine, iron, manganese, magnesium, molybdenum, phosphorus, potassium, selenium, sodium, sulfur, and zinc. Some additional important nutrients, the marine omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA), are discussed here, although they are not known as vitamins. Nine essential dietary amino acids are also important for the synthesis of proteins and hormones (2) but will not be discussed. The abbreviated term V/M is used throughout this presentation because it refers to a coherent category of nutrients, although only a few minerals/elements are discussed.

Most of the world's population—even in developed countries—consume many of the V/M at levels below those recommended (3, 4). Using as reference the estimated average requirement (EAR) values [the intake level for a nutrient at which the needs of half of the healthy population is adequate and half is

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inadequate (5, 6)], the following numbers are given as examples of the high percentages of the United States population ingesting V/M quantities below the EAR (including fortifications and supplements): vitamin D, 70%; vitamin E, 60%; magnesium, 45%; calcium, 38%; vitamin K, 35%; vitamin A, 34%; vitamin C, 25%; zinc, 8%; vitamin B6, 8%; folate, 8% (7). Intakes of the marine omega-3 fatty acids DHA and EPA are also remarkably low in the United States population; an EAR has not been set (8). A varied and balanced diet could provide enough V/M for a healthier and longer life. A diet containing much of its calories as refined foods and sugar is deficient in V/M and leads to an unhealthy and shorter life.

The association or causality between various diseases of aging and a number of V/M deficiencies is analyzed here by screening the literature and using as criteria clinical trials, epidemiology, Mendelian randomization studies, and biochemical and medical literature. A sampling of the literature covering the link of various diseases with V/M deficiencies is provided in *SI Appendix, SI-1 Vitamin and Mineral Deficiences*.

Triage Theory

The triage theory (1) provides a unifying rationale for why modest V/M deficiencies—insufficient to elicit overt symptoms of severe deficiency—might contribute significantly to the aging process and the diseases of aging. Briefly, the triage theory posits that a strategic rationing response has been selected through evolution, which ensures that when a moderate shortage of a V/M is encountered, the scarce V/M is preferentially retained by those V/M-dependent proteins/enzymes that are essential for survival and reproduction, such as proteins essential for early development and immediate survival (i.e., "survival proteins"). At the same time, proteins/enzymes needed for maintaining long-term health by preventing insidious damage are starved for that V/M and become increasingly inactive, thus leading to an increase in diseases of aging. A major aspect of degenerative aging is that the damage is insidious and clinically not obvious because it accumulates slowly over time and is apparent only later in life. The connection to V/M shortages is underappreciated.

This concept of triage has been buttressed by our analyses of vitamin K and the element selenium (9, 10). Vitamin K-dependent proteins could be categorized into those required for short-term survival (primarily blood-clotting functions) and those involved in long-term health. A similar triage rationing was found for selenium-dependent proteins (10). Recent human studies provide additional support for the triage theory with respect to vitamin K and selenium (*SI Appendix, SI-2 Triage Theory*). It is noteworthy that in both of these cases about half of the proteins are affected negatively by a V/M shortage, suggesting that a large price could be paid in terms of accelerated aging by such a shortage.

The mechanisms by which triage rationing occurs vary: for vitamin K the proteins are found in physically unconnected tissues. In the case of selenium the rationing is based on the use of two different transfer RNAs (tRNAs) controlled by a modified base in the tRNA. Thus, different mechanisms were adopted for the same ultimate outcome in these two examples, suggesting that they evolved independently.

Although the triage theory (1, 9, 10) was originally thought of as a cofactor-rationing system, upon further consideration it should be more broadly construed to include a larger variety of components that are not enzyme cofactors, but are still essential elements in triage rationing. The trading-off of metabolic resources to achieve a balance between somatic maintenance and reproductive fitness was proposed in an evolutionary theory of why we age (11). The triage theory provides a mechanism for achieving such a trade-off.

Rethinking Vitamins: Longevity Proteins and Vitamins

Vitamins and essential minerals are usually thought of as compounds crucial for survival or protection against severe ill health, as shown by their dramatic short-term effect upon removal from the diet; most are necessary for critical metabolic functions. The role of vitamins in healthy aging has been less appreciated. I am introducing two concepts inherent in the triage-rationing mechanism: longevity proteins and longevity vitamins.

Longevity Proteins and Survival Proteins. Among the insights derived from the triage theory are the following concepts: (*i*) not all proteins/enzymes are affected equally by a V/M deficiency; (*ii*) not all V/M are exclusively needed for short-term survival; (*iii*) adequate V/M throughout life plays an important role in healthy aging. I propose that during triage rationing proteins that are sacrificed to allow for survival belong to a category with the specific function of protecting against diseases of aging. I propose to name them longevity proteins. In contrast, those needed for short-term survival and reproduction, and thus preferentially supplied with a V/M necessary for their function (besides being also necessary for later health) are referred to as "survival enzymes/proteins." A fraction of the cofactor-requiring proteins that are subject to triage rationing are not technically enzymes (e.g., regulatory or structural proteins).

Longevity Vitamins. A redefinition of vitamins emerges from the definition of longevity proteins: the concept that the dietary compounds needed for the function of longevity proteins belong to a special category—that is, longevity vitamins—the shortage of which result in damage that is cumulative and insidious. Thus, vitamins may be divided into two general categories: (*i*) supporting both survival and longevity proteins (as defined above), and thus subject to triage rationing; and (*ii*) supporting health without emphasis on early survival, but with their shortage leading continuously to accelerated aging, which may or may not be rationed (e.g., antioxidants, many of which are not protein cofactors). Some of those that are rationed may not involve interaction with a protein (e.g., carotenoids).

In addition, I propose that an important consequence of this insight is the likely existence of compounds that are needed only for longevity, and therefore are not essential for short-term survival. It is likely that dietary compounds that are not essential for survival and are used exclusively for protecting and improving healthy longevity would not yet have been recognized as V/M, because the effects of their deficiency would have been evident only in the form of insidious late damage. Evidence for 10 putative longevity vitamins is presented below.

Survival V/M That Are also Longevity V/M

Inherent in the triage theory is the concept that most V/M necessary for the proper function of longevity proteins/enzymes are also survival V/M, having been originally discovered as cofactors for survival proteins. Thus, these V/M have two effects: on short-term survival and on long-term health. Besides the examples of vitamin K and selenium as being both essential and longevity V/M, three additional examples of V/M that have both effects are vitamin D, marine omega-3 fatty acids (DHA/EPA), and magnesium. The levels of each of these are inadequate in a large percentage of the American population, and these deficiencies are a major contributor to unhealthy aging.

Vitamin D. Vitamin D levels are inadequate in 70% of the United States population. Almost all dark-skinned people residing in northern latitudes are particularly deficient (12, 13). Vitamin D was long considered responsible only for protecting against rickets, but it has now been shown to be involved in a myriad of functions. A cholesterol derivative, 7-dehydro-cholesterol, is converted by

UV light to a precursor of vitamin D steroid hormone. Then the final steroid hormone binds to a protein, the vitamin D receptor protein; the latter interacts with a 12-base regulatory sequence in vitamin D receptor-dependent genes and regulates them either in a positive or negative fashion (12, 13). About 2,700 such binding sites have been found in the human genome as interacting with the vitamin D receptor protein (14). Extensive evidence shows that vitamin D deficiency causes—or has been associated with—a large number of diseases that affect healthy aging, such as all-cause mortality, cancer, cardiovascular disease (CVD), diabetes, brain function, and so forth. Considering this high level of deficiency and the important implications of vitamin D interactions, it is particularly important to tune up metabolism (15) with respect to vitamin D. See *SI Appendix, SI-3 Survival V/M That Are also Longevity V/M* for the large literature on vitamin D clinical trials and Mendelian randomization studies.

Supplementation with vitamin D, which would prevent and relieve some of these problems, has been discouraged for two reasons: fear of toxicity (in older studies) and numerous inadequate clinical trials. Newer evidence on the effect of vitamin D on all-cause mortality supersedes these toxicity studies, concluding that there was no increased risk even when blood levels of 25(OH)D were as high as 100 ng/mL (16–18).

The use of randomized clinical trials (RCTs) for studying the effect of nutrients, as opposed to drug trials, can be subject to misinterpretation unless the level of the nutrient is measured both before supplementation starts and at its end. This precaution is necessary because many of the subjects may not be deficient in the nutrient being tested and the amount supplemented may be insufficient to raise levels adequately. The absence of such measurements can lead to erroneous negative results, as shown for various RCTs for vitamin D (19) and as pointed out repeatedly in the nutrition literature (20–28). Many conclusions, both in medical journals (e.g., refs. 29 and 30) and in books (e.g., ref. 31), that supplemental vitamins are ineffective in performing some function generally ascribed to them, should be taken skeptically if the RCT did not include measurements of the vitamin.

Thus, it is clear that vitamin D performs more than just its initially assigned function of maintaining bone health. It is important for a healthy long life, and thus it is a longevity vitamin.

Marine Omega-3 Fatty Acids, DHA and EPA. The intake of these compounds is inadequate in most of the United States population (8). Low EPA and DHA levels in red blood cells were found to be associated with increased all-cause mortality in a study of 6,501 elderly women followed for 14.9 y (32). A meta-analysis reported that each 1% increase in plasma DHA/EPA was linked with a 20% decreased risk in all-cause mortality (33).

DHA/EPA are present in high levels in the central nervous system and are important for brain and retinal structure and function (34). In an RCT on first-episode schizophrenia patients, omega-3 fatty acids supplementation prevented cortical loss of gray matter thickness and promises a possible treatment for schizophrenia (35). The role of DHA in aging, Alzheimer, Parkinson, schizophrenia, bipolar, and depression have been recently reviewed (34).

Low blood levels of DHA/EPA were shown in a 5-y study to be associated with a faster rate of telomere shortening, a marker of cell aging (36). Supplemental fish oil (2.5 g/d) slowed telomere shortening and lowered biomarkers of oxidation in older adults (37). Daily supplemental DHA (2 g/d) increased the rate of clearance of amyloid plaques in people with mild cognitive impairment (38). DHA/EPA are important for vitamin D steroid hormone effectiveness (13). Evidence of their role in reducing the risk of heart disease has been obtained (39, 40). Linolenic acid (omega-3) is now considered an essential fatty acid, but it is still unclear whether it is just needed as a precursor of DHA/EPA, which are inefficiently made from it.

Magnesium. Mg is present in the center of the chlorophyll molecule, with plants being a major dietary source, together with whole grains, nuts, and seeds (41). Mg deficiency affects about 45% of the United States population and has been associated with increased all-cause mortality, poor DNA repair capacity, increased risk of lung cancer and various other kinds of cancer, heart disease, telomere shortening, and risk of stroke (*SI Appendix, SI-3 Survival V/M That Are also Longevity V/M*).

A recent review on the subclinical effects of Mg deficiency makes the case that this deficiency is a principal driver of CVD, a worldwide underrecognized problem, and thus that it is a major public health crisis (42). Mg is required to convert vitamin D to its active steroid hormone form (43).

In conclusion, these three examples of V/M deficiencies, together with the vitamin K and selenium studies, provide considerable evidence that these compounds fit the definition of longevity V/M, as well as being essential for survival, and that optimizing their intake offers a way to lengthen healthy longevity.

Conditional Vitamins

A conditional vitamin is synthesized by the body, but not at a level that is sufficient to optimize metabolism.

Choline. Choline was the first example of a conditional vitamin (44): only 11% of women achieve the recommended intake and the average intakes for the population are half to two-thirds of this recommendation (45); severe choline deficiency results in DNA strand breaks in rodents, alterations to epigenetic markers and histones, and affects brain development (46–48).

Taurine (2-Aminoethanesulfonic Acid). Taurine is another example of a conditional vitamin because it is synthesized by animals (including humans), but not in sufficient amounts. It has been shown to be important in preventing numerous health problems, such as CVD, brain function, diabetes, and mitochondrial diseases, as summarized below. Because of taurine's extensive involvement in health problems that lead to long-term damage, it is proposed here that it is also a longevity vitamin.

The synthesis of taurine involves cysteine decarboxylation and sulfhydryl oxidation. The rate of its biosynthesis is species-dependent, with a low level in humans, compared with rodents (which led to the suggestion that supplementation might be beneficial) (49). It is located in the cytosol and in mitochondria and it is present in virtually all human tissues at millimolar concentrations; it is especially high in electrically excitable and secretory tissues and in platelets. A 70-kg human contains about 70 g of taurine (50). An excellent review of all of the earlier work on taurine is available in Huxtable (50). Most of taurine is acquired from the diet, mainly from fish and other seafood, seaweed, eggs, and dark-meat poultry (51).

Taurine is particularly important in the mitochondria, where it is present as 5-taurinomethyl-uridine in tRNA-leu and tRNA-trp, and as 5-taurinomethyl-2-thiouridine in tRNA-glu, tRNA-gln, and tRNA-lys. In all five tRNAs, it is located in the wobble position, where it functions to read accurately alternate codons in the mitochondrial genome (52). A taurine modification defect in mitochondrial tRNA is associated with the mitochondrial diseases MELAS (mitochondrial encephalopathy, encephalopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonus epilepsy with ragged-red fibers) (52), suggesting causality, and also that a taurine deficiency could result in the same diseases.

Because of the involvement of mitochondria in energy production, there has been much interest in taurine in sports medicine in humans with reference to exercise-induced fatigue and recovery, as has been reviewed previously (53). In addition, a strong case has been made that taurine is the main buffer in mitochondria (54) and that it moderates mitochondrial oxidant production (55).

Another possibly important function of taurine is its detoxification of chloramine (a very toxic membrane-soluble oxidant) via its conversion to taurine-chloramine (56, 57).

Examples of several important insidious long-term pathologies that taurine would protect against are: CVD, brain dysfunction, and diabetes. Taurine effects on CVD have been examined by numerous RCTs and have been reviewed previously (51). Taurine supplementation lowers blood pressure, improves vascular function, and raises plasma hydrogen sulfide levels as shown in a recent RCT with prehypertension patients (58). Taurine consumption was the most significant factor associated with reduced risk of ischemic heart disease (IHD) in two international epidemiological studies of CVD in 61 populations (25 countries; $n = 14{,}000$): Japanese people in Okinawa had the highest taurine dietary intake and the lowest incidence of IHD and longest lifespan. In contrast, Japanese immigrants in Brazil who eat little seafood, but more meat and salt, had a 17-y shorter lifespan as a consequence of a very high IHD mortality (59). Other human clinical studies showed that taurine decreases platelet aggregation, serum cholesterol levels, LDL/triglyceride levels, and enhances cardiac function (60).

Taurine plays an important role in brain development, including neuronal proliferation, stem cell proliferation, and differentiation; it has no toxic effects in humans (61). It is a neuromodulator in the central nervous system: it activates the GABA- and glycine-insensitive chloride channel and it inhibits the *N*-methyl-D-aspartate receptor. It is also neuroprotective and has a role in neural development and neurogenesis; it was shown in an RCT that symptoms of psychopathology were improved by its administration in patients with first-episode psychosis (62).

Diabetic remediation by taurine has been reviewed previously (63, 64). Its supplementation remediates diabetic pathologies, including retinopathy, neuropathy, nephropathy, cardiopathy, atherosclerosis, altered platelet aggregation, and endothelial dysfunction (65). In patients with type 1 and type 2 diabetes the taurine transporter is up-regulated in mononuclear blood cells, indicating that increased levels of taurine are sought by the cell (66, 67). In rats, taurine reduces oxidative stress caused by diabetes (68, 69).

Taurine is important for fetal development, because the human fetus cannot synthesize taurine, which is provided by the mother via the taurine transporter, and it is necessary for organ development and protects against development of type 2 diabetes (70). Therefore, taurine is also a survival vitamin. Transport of taurine (53) is required for normal development of numerous fetal tissues in several experimental animals. Taurine functions as an osmolyte; it was shown to be important in that respect in a variety of species, including rodent investigations that are consistent with the above results on humans (70, 71) (*SI Appendix, SI-4 Conditional Vitamins*).

Taurine is well established as an important conditional vitamin for survival functions and for healthy longevity in both humans and experimental animals. I expect that a large class of new conditional vitamins will be discovered. Possible candidates are lipoic acid, ubiquinone, and carnitine.

Putative Longevity Vitamins: Ergothionine, Pyrroloquinoline Quinone, Queuine, Carotenoids

I propose that many of the known vitamins and minerals have, besides a "survival" function, aging-delaying ("longevity") functions as well. I also propose that other dietary biochemicals, not officially recognized as vitamins or as having age-delaying functions, have a positive age-delaying effect. Several such compounds are discussed as candidates for putative longevity vitamins: the fungal antioxidant ergothioneine (ESH); the bacterial compounds pyrroloquinoline quinone (PQQ) and queuine; and seven plant carotenoids. Among these putative longevity vitamins are specialized dietary antioxidants (ESH, PQQ, and carotenoids) that reduce the accumulation of long-term oxidative damage (besides other important functions) and are not normally classified as "survival vitamins." It should be noted that within this category vitamin C is categorized as a survival vitamin because, in addition to being an antioxidant, it also functions as a cofactor for survival proteins. On the other hand, vitamin E is a fat-soluble, free-radical scavenger/chain-breaking antioxidant, and is not required for any known protein/enzyme functions. Neither are discussed further. Other important functions, besides protecting against oxidation, are associated with longevity. The mechanisms by which the body prevents insidious aging-related damage are likely to be numerous.

Ergothioneine. ESH is present in the human diet. It is synthesized by most mushrooms (72), cyanobacteria, and many types of soil bacteria (73, 74), but not by plants or animals. Various plant foods contain small amounts of ESH taken up from the soil; animals that eat such plants contain ESH in their flesh. The edible fungi synthesize ESH to concentrations varying from a very high level (>100 mg/kg wet weight in oyster and king boletus mushrooms) to a much lower level (0.5 mg/kg) in the white-button commercial mushrooms, which is most commonly eaten. A detailed analysis suggests that mushrooms are a major ESH source in Europe (75). Foods known to have moderate levels of ESH (1 mg/kg wet weight) include beef, pork, lamb, and chicken. Oat bran, black turtle bean, and red kidney bean contain >3 mg/kg (72, 76).

ESH has been shown to be present in almost all human cell and tissue types, often at millimolar levels in the brain, bone marrow, lens and cornea of the eye, and erythrocytes (77, 78), where it appears to play a significant role as an antioxidant. Its function as a specialized antioxidant is thought to be implicated in CVD prevention and its redox chemistry has been reviewed previously (79, 80). Its levels decrease significantly with age past 80 y, and significantly lower levels were found in individuals with mild cognitive impairment (81). It has been suggested that ESH acts as an adaptive antioxidant for the protection of injured tissues (82). Rheumatoid arthritis has been associated with increased ESH levels in red blood cells in a case-controlled study (83). It is also present in high concentrations in mitochondria, a major source of oxidants, and it has been suggested that it may be a vitamin (84).

ESH in mammals is taken up by a specialized transporter, OCTN1 protein (85, 86), which appears to have been selected for in the European transition from hunter-gatherers to agriculturalists (87). Lack of this transporter results in oxidative damage to proteins, lipids, and DNA, and higher levels of mortality in human cells (84). Dysfunctional haplotypes of the ESH transporter gene are associated with Crohn's disease (88, 89). The ESH transporter is essential because deletion of its gene in mice (90) or zebra fish (91) results in oxidative damage to DNA and lipids. All of these characteristics suggest an involvement in healthy aging. A likely mechanism of ESH action appears in *SI Appendix, SI-5 Putative Longevity Vitamins*.

The presence of ESH in human tissues, the essentiality of its transport system, its possible involvement in CVD prevention, its antioxidant, and cytoprotectant activities, all suggest that ESH is a putative longevity vitamin.

Pyrroloquinoline Quinone. PQQ is made by many species of bacteria, but not by animals or plants. It is a cofactor for several bacterial dehydrogenases, such as glucose and methanol dehydrogenases (92, 93). It is synthesized by soil bacteria, enters plants from the soil (94), and thus enters human diets; it was detected in every sample of fruits and vegetables tested at levels 5–10 times higher than in human tissues and fluids. PQQ is an important plant growth factor imported from rhizobacteria (95). It is a powerful antioxidant and is much more stable than ascorbic acid; in redox cycling, PQQ has 20,000 potential catalytic cycles, compared with 4 for ascorbic acid (92).

The health benefits of PQQ in humans have been reviewed recently, including for diabetes, antioxidant activity, neuroprotection, cognition (96), and lowering the level of C-reactive protein (i.e., inflammation). In addition, PQQ supplementation improved antioxidant potential and decreased the levels of mitochondrial-related intermediates and metabolites in urine, providing support for previous studies that demonstrated that PQQ improved mitochondrial efficiency (97).

PQQ has been repeatedly suggested to be a vitamin, although arguments have been raised against it (92). The case for its being classified as a vitamin has become stronger due to a recent breakthrough study (98) of five mouse proteins that bind PQQ. This work confirmed that the activity of at least one mammalian enzyme, rabbit lactic dehydrogenase-A, depends on PQQ to catalyze the key conversion of lactate to pyruvate at physiological PQQ levels (98). This activity enables mitochondria, when limited in activity by reductive stress (i.e., high NADH/NAD ratio), to synthesize more ATP as an alternative to exporting lactate. PQQ has also been shown to induce mitochondrial biogenesis at low physiological levels (~250 μg/kg in rat) through the proliferator-activated receptor-γ coactivator-1 α (PGC-1α) in peroxisomes (99, 100). Experiments in cats and rodents on PQQ are numerous and confirmatory (*SI Appendix, SI-5 Putative Longevity Vitamins*).

PQQ is promising as a longevity vitamin in humans. It is necessary for mitochondrial health (although most of the evidence for the latter comes from rodent studies).

Queuine. Queuine is an evolutionarily ancient compound (101). It is a 7-deazaguanine derivative present in bacteria, which are unique in their ability to synthesize it and pass it on to plants and animals (102). Detectable amounts of queuine have been identified in tomatoes, wheat, coconut water, and milk from humans, cows, and goats (102). Humans and mice recover queuine from either ingested food or the gut flora. All eukaryotic organisms, including humans, convert queuine to queuosine by placing it in the wobble position (anticodon) of several tRNAs: aspartic acid, asparagine, histidine, and tyrosine (101, 103, 104). For details, see *SI Appendix, SI-5 Putative Longevity Vitamins*.

Queuine deficiency, uptake, and function have been reviewed (102). It is notable that eukaryotes have retained a number of dedicated proteins for queuine utilization, which include a conserved mitochondrial tRNA transglycosylase, thus indicating its essentiality (105). The cellular uptake of queuine appears to occur through a dedicated transporter (102). Queuine deficiency in human cells in vitro and in animals results in a reduced level of the cofactor tetrahydrobiopterin, BH4 (106). BH4 is a necessary cofactor for the conversion of phenylalanine to tyrosine, of tryptophan to serotonin, of tyrosine to DOPA (which gets converted into epinephrine and norepinephrine), of arginine to NO, and for the oxidation of alkyl glycerol lipids (107, 108). The essentiality of BH4 for the hydroxylation of tryptophan to produce serotonin could be of relevance to numerous neurological conditions, especially considering serotonin's role as a social hormone controlling executive function, and its relevance to autism, attention deficit/hyperactivity disorder, bipolar, and schizophrenia (12, 13, 109–111). Queuine-deficient mice become tyrosine-deficient, dying within 18 d of its withdrawal (112), despite the fact that tyrosine is a nonessential amino acid, presumably because it results in BH4 deficiency.

A recent key paper (113) shows that queuine and a synthetic analog have been proven effective in a mouse model of multiple sclerosis in eliciting full remission from the disease. Animals deficient in the tRNA guanine transglycosylase, and thereby incapable of modifying tRNA, fail to respond to therapy, implying that modulation of protein translation is the principal means through which the therapeutic effect is elicited.

The finding that queuine is located in the wobble position of tRNA (an ancient molecule), that a number of dedicated enzymes for queuine utilization have been strongly conserved in eukaryotes, the existence of a dedicated transporter, the effect on BH4 synthesis, together with its broad distribution, all suggest that queuine should be classified as a putative longevity vitamin. It will be desirable to obtain evidence of human pathologies, and thus of unhealthy aging, consequent to a lack of queuine.

Carotenoids. There are ~600 carotenoids synthesized by plants, but not by animals. They act as antioxidant pigments in all plants and usually contain 11 conjugated double bonds, which accounts for their yellow/orange/red colors. All photosynthetic plants synthesize carotenoids to quench singlet oxygen, a highly energetic and toxic form of oxygen created in cells by strong light. The toxicity of singlet oxygen is due to its ability to oxidize proteins, lipids, and nucleic acids, which can lead to cell death (114). The extra singlet oxygen energy is dissipated as heat via the long chain of conjugated double bonds in these compounds. They mimic enzymes in that one molecule of carotenoid can destroy hundreds of molecules of singlet oxygen. It should be noted that because the carotenoid family is very large, carotenoids related to each other may replace each other to perform the same functions, depending on the individual diet.

The following six carotenoids account for 95% of the carotenoids found in American blood and brain: lutein, zeaxanthin, lycopene, α- and β-carotene, and β-cryptoxanthin. The importance for health of a seventh carotenoid, the powerful marine carotenoid astaxanthin, which contains 13 conjugated double bonds, is also discussed (*SI Appendix, SI-5 Putative Longevity Vitamins*). These are increasingly being accepted as vitamin-like nutrients (115). There is good evidence that these carotenoids help optimize a healthy lifespan: low intake of these carotenoids has been associated with all-cause mortality, macular degeneration and associated blindness, cognitive decline, CVD, various types of cancer, metabolic syndrome, oxidative damage to DNA, high blood pressure, hearing loss, decreased visual acuity, inflammation, immune decay, and cognitive decay. It is well known that α- and β-carotene, and β-cryptoxanthin are precursors of vitamin A; thus, some of the health effects upon their deficiency may be due to insufficient vitamin A. A description of their chemical nature and properties, together with a summary of the analysis of their link to diseases of aging, appears in *SI Appendix, SI-5 Putative Longevity Vitamins*.

Carotenoids are included among putative longevity vitamins because of the evidence that they protect long-term health. The strength of the evidence varies, but they deserve more attention for their role for achieving a healthy longevity.

Discussion

Prolonging good health while aging is an important issue in a world with large increases in life expectancy. Mechanistic,

genetic, and epidemiological evidence suggests that the metabolic trade-off occurring upon a V/M shortage results in an accumulation of insidious damage and aging-associated diseases. Here I propose that the relatively simple approach of securing sufficient intake of well-known dietary V/M, plus taurine, plus the 10 putative longevity vitamins introduced here, could lead to healthy aging by "tuning-up metabolism" (15) and promoting metabolic harmony and health. Other important nutrients will undoubtedly be found in the future. Because about one-quarter of enzymes require 1 of the ~30 survival and longevity V/M as a cofactor in complex metabolic networks (116), it is clearly important that the organism be properly supplied with such compounds. By optimizing survival and longevity V/M intake throughout life, premature, insidious, and increased risk of degenerative diseases may in large part be preventable.

V/M deficiencies, as indicated by intakes below the EAR, are common in the United States (6, 7, 117) and around the globe, especially among the poor, children, adolescents, the obese, and the elderly. According to the official National Academy of Medicine measure of inadequacy, most of the United States population is below the EAR for one or more essential V/M. It should be noted that the official definition of EAR does not take into consideration that the "healthy" population sampled may be only "apparently healthy" because evidence is provided herein that it is actually aging faster due to long-term triage effects. Therefore, official EAR values might actually have been set too low, because they did not take long-term triage effects into account, and thus more people would be erroneously considered "adequate." Thus, a concept derived from this proposal is that EAR values should be set for longevity V/M by taking into account long-term effects of longevity V/M.

Evidence is accumulating that lack of foods that are particularly nutrient-rich is a contributor to diseases of aging. "Healthy foods" are nutrient-dense, containing high levels of V/M, fiber, and longevity vitamins, relative to calories (5): for example, nuts/seeds, eggs, seafood, vegetables, and fruits (118–120). These foods are enriched in vitamins to nourish the next generation. Humans should be able to stay healthier longer during old age if nourished appropriately. It is important to link a mechanistic understanding of the diseases of aging to the consumption of individual nutrients and to their synergies (121, 122).

Our emphasis on insidious damage does not imply that V/M deficiency is the only major cause of the degenerative diseases of aging. For example, many types of cancers, dementias, and other degenerative diseases may be caused by pathogens (123) or genetics. However, V/M intervention might also help prevent some of these, as for example, by protecting the immune system (124), which defends against pathogens in elderly individuals.

Although V/M are generally understood to be important for health, it is not usually understood that other substances—usually referred to as micronutrients, bioactives, and so forth—are equally important for health, although not resulting in acute signs upon deficiency. Thus, I propose to call these compounds, collectively, longevity vitamins, in the interest of clarity and public health.

Some of the insidious damage due to a nutrient shortage may be reversible once the V/M intake is increased. However, some insidious damage would not be reversible if it were due to a mutational event, such as loss of a chromosome (e.g., in the case of vitamin K deficiency, as mimicked by TGFβI inactivation) or, as in the case of DNA damage, resulting from mutagenic oxidant release consequent to shortage of the antioxidant selenium.

Obese individuals are paricularly deficient in V/M (125–130), which is a likely explanation, among others, for a decrease in longevity through an increased frequency of every age-associated disease that has been examined, including cancer (131), heart disease (132–134), brain decay (135–137), and immune decay (138). The health and longevity of the obese would benefit greatly from an improvement in their V/M intake.

It should be noted that plants contain a large number of bioactive chemicals, which are present in our diets, as for example 8,000 different flavonoids (139). Flavonoids function as "nature's pesticides," the purpose of which is to protect plants from predators (140); many have beneficial (or toxic) effects in humans at some dose and may function by inducing hormetic mechanisms (141). There is no evidence, to my knowledge, that these compounds act as vitamins.

The involvement of tRNA-modified bases in triage rationing in the cases of selenium (10) and of taurine and queuine provides three examples of such a mechanism of rationing. The use of tRNA-modified bases suggests that this is an ancient mechanism dating to the RNA world that presumably preceded the DNA world (142) and may involve many aspects of metabolism.

An important concept relative to the use of vitamins for health is the fact that over 50 human genetic diseases can be ameliorated by the administration of high doses of supplements (143). Supplementation raises the concentration of the needed coenzyme to levels that overcome a defect in the enzyme-binding site (which is likely to be deformed by mutation or aging-related membrane rigidity) (144), besides possibly affecting the abundance and stability of some proteins. Some of the mitochondrial decay accompanying aging may be due to membrane rigidity and be remediable, as shown in rats (145). The remediation of proteins deformed by mutation or aging provides a simple way to improve health and longevity (144).

The Future

Eventually, the age of preventive medicine will take into consideration the major effects of V/M components, in addition to genetic factors. The optimization of the nutritional status and of the level of various biomarkers could be determined by each individual, perhaps through an analyzer machine using a finger-prick of blood (146). There is a need for the development of assays providing a range of the V/M levels required to keep enzymes/proteins optimally functional. Assays are also needed for the connection of deficiencies of longevity vitamins with their consequent respective pathologies. Measurements of the activity of longevity proteins are essential for detection of the functional effects of a low intake of each V/M. Two examples of consequences of V/M insufficiency, which are measurable, are increased DNA damage and mitochondrial decay. Understanding the full spectrum of longevity V/M will be augmented in future years.

The prevention of the degenerative diseases of aging is a different science than curing disease: it involves expertise in metabolism, nutrition, biochemistry, and genetic regulatory elements and polymorphisms. This approach is critical for lowering medical costs: it has been estimated that the European Union would save €4 billion from osteoporosis alone, by using vitamin D and calcium supplementation (147). The additional benefits derived from an improved V/M utilization would increase savings.

In conclusion, in addition to keeping physically fit, the low-hanging fruit in prolonging a healthy aging lies in optimizing V/M intake (e.g., refs. 12, 13, 15, 130, and 148).

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