

Review Article

Prevention of Mutation, Cancer, and Other Age-Associated Diseases by Optimizing Micronutrient Intake

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I review three of our research efforts which suggest that optimizing micronutrient intake will in turn optimize metabolism, resulting in decreased DNA damage and less cancer as well as other degenerative diseases of aging. (1) Research on delay of the mitochondrial decay of aging, including release of mutagenic oxidants, by supplementing rats with lipoic acid and acetyl carnitine. (2) The triage theory, which posits that modest micronutrient deficiencies (common in much of the population) accelerate molecular aging, including DNA damage, mitochondrial decay, and supportive evidence for the theory, including an in-depth analysis of vitamin K that suggests the importance of achieving optimal micronutrient intake for longevity. (3) The finding that decreased enzyme binding constants (increased K_m) for coenzymes (or substrates) can result from protein deformation and loss of function due to an age-related decline in membrane fluidity, or to polymorphisms or mutation. The loss of enzyme function can be compensated by a high dietary intake of any of the B vitamins, which increases the level of the vitamin-derived coenzyme. This dietary remediation illustrates the importance of understanding the effects of age and polymorphisms on optimal micronutrient requirements. Optimizing micronutrient intake could have a major effect on the prevention of cancer and other degenerative diseases of aging.

1. Lipoic Acid and Acetyl-Carnitine Supplements Decrease the Oxidative Mitochondrial Decay of Aging

Mitochondrial decay appears to be a major contributor to aging and its associated degenerative diseases including cancer and neural decay [1, 2]. Mitochondria from old rats compared with those from young rats generate increased amounts of mutagenic [3–5] oxidant by-products [6] and have decreased membrane potential, respiratory control ratio, cellular oxygen consumption, and cardiolipin (a key lipid found in mitochondria). Oxidative damage to DNA, RNA, proteins, and mitochondrial membrane lipids contributes to this decay [6–10] and leads to functional decline of mitochondria, cells, tissues, and eventually organs such as the brain, with an accompanying loss of cognition and ambulatory activity [6–10].

Decreased capacity to produce ATP and increased oxidant production are two properties of aging mitochondria

supported by multiple lines of direct and indirect observations. First, the analysis of gene expression profiles in mice showed significant age-associated declines in the mRNA levels of mitochondrially encoded subunits of complex I, III, IV, and V in old compared to young mice [11]. Second, in addition to reduced gene expression, the levels of mutagenic [3, 4] aldehydes [12] and oxidants increase in aging tissues.

The importance of optimizing metabolic function to prevent mitochondrial decay is illustrated by feeding the mitochondrial metabolites acetyl carnitine (ALC) [13–15] and R-alpha lipoic acid (LA) [16] to old rats. Carnitine is used for transporting fatty acids into the mitochondria; the main short-chain acyl-carnitine is ALC [17]. In humans at rest, ALC accounts for roughly a quarter of total carnitine in plasma, muscle, and liver tissues [17]. LA is a mitochondrial coenzyme and is preferentially reduced in the mitochondria to a potent antioxidant. LA is also an effective inducer of the transcription factor Nrf2, which in turn induces the glutathione synthesis enzymes [18–20]. Nrf2 induces over

200 phase-2 antioxidant and thiol-protective enzymes [21, 22]. ALC and LA, when added as a supplement, can act in some cases synergistically, to restore much of the lost mitochondrial function in old rats [6–9].

One possible mechanism of mitochondrial decay is that with age, stiffer membranes due to lipid oxidation or increased oxidative damage to mitochondrial proteins cause structural deformation of key enzymes such as carnitine acyl transferase that lowers their affinity for the enzyme substrate [9]. Feeding old rats the substrate ALC with LA for a few weeks decreases oxidative damage, allowing the synthesis of new carnitine acyl transferase with normal binding affinity (K_m) [9]. This partially restores mitochondrial function, decreases mutagenic oxidants, neuronal RNA oxidation, and mutagenic aldehydes, and increases rat ambulatory activity and cognition [6–9]. ALC and LA are not usually thought of as micronutrients, as they can be synthesized in the body, but they are illustrative of many normal metabolites that decline with age and may be beneficial as supplements in the elderly.

Park et al. [23] used DNA microarrays to identify transcriptional markers of aging that are differentially expressed in young versus old mice of multiple inbred strains. They then fed the mice various metabolites, mostly antioxidants, to see if they would oppose these transcriptional markers of aging, comparing effectiveness to caloric restriction, a known potent method for delaying aging. ALC was as effective as caloric restriction in the heart and LA was as effective in the cerebellum. These experiments suggest that ALC + LA is an effective caloric restriction mimetic and that tuning up metabolism may help in slowing down the aging process. The tissue specific effects of caloric restriction-mimetic agents suggest that a combinatory approach may be needed.

2. Triage Theory Suggests a Cause of Much Preventable Mutation and Cancer

The “trriage theory” [24–26] provides a unifying rationale for a causal link between chronic modest deficiency of a micronutrient (~40 essential minerals, vitamins, amino acids, and fatty acids) and the many degenerative diseases accompanying aging such as cancer, immune dysfunction, cognitive decline, cardiovascular disease, and stroke. If the theory is correct, the incidence of these diseases might be reduced by an inexpensive micronutrient intervention [24–26].

Triage theory [24, 25] posits that during evolution, as a result of periods of shortage of micronutrients required by various proteins for function, nature was selected for a rebalancing of metabolism (e.g., by selection for strong micronutrient binding constants for critical proteins). This rebalancing ensured survival of the organism at the expense of metabolism whose lack caused the accumulation of insidious damage leading to longer-term consequences, that I proposed including chronic diseases of aging. That nature may have developed such a system is logically consistent with the consensus that natural selection favors short-term survival for reproduction over long-term health [27]. During evolution micronutrient shortages were likely to be

very common. For example, the 15 essential minerals are not distributed evenly on the earth; dietary sources and availability also fluctuated markedly [28].

The triage theory predicts that optimizing intake of the ~40 essential micronutrients will reduce the risk of chronic diseases associated with aging and increase lifespan [24]. Micronutrients are remarkably inexpensive. Micronutrient intakes below recommended levels are unusually widespread in poor countries, but also in the US population in all segments of society, especially the poor, children, adolescents, the obese, and the elderly. High consumption of calorie-rich, micronutrient-poor unbalanced diets exacerbates the problem [24]. For example, over half of the US population have inadequate intakes of magnesium [24], almost all African-Americans are extremely low in vitamin D [29], and much of the population is low in a variety of other micronutrients, (e.g., omega-3 fatty acids, potassium, calcium, vitamin C, vitamin E, vitamin K) [24, 30, 31]. There is little societal concern because no overt pathologies have been associated with marginal to moderate levels of deficiency. The triage theory predicts that the pathology is insidious, but we believe that it is measurable. We hypothesize that two of the many insidious, but measurable, consequences of moderate micronutrient inadequacy are increased DNA damage (future cancer) and mitochondrial decay (mutagenic oxidant release, future cancer, and cognitive dysfunction) as aspects of a triage response. These consequences are known to increase with age. In addition, evidence from our own work and that of others, as briefly reviewed below, indicates that sensitive assays targeted at these endpoints have a high likelihood of detecting changes in individuals with moderate micronutrient deficiencies. Other age-related diseases, such as cardiovascular disease and immune dysfunction [25] are also increased by micronutrient deficiencies and are discussed elsewhere [25, 30].

2.1. Vitamin K as an Example of the Utility of Triage Theory [30]. For 16 known vitamin K-dependent (VKD) proteins, we evaluated the relative lethality of 11 known mouse knockout mutants to categorize essentiality. Results indicated that 5 VKD proteins required for coagulation had critical functions (knockouts were embryonic lethal), whereas the knockouts of 5 less critical VKD proteins [osteocalcin, matrix Gla protein (Mgp), growth arrest specific protein 6 (Gas6), transforming growth factor β -inducible protein (Tgfb1 or β ig-h3), and periostin] survived at least through weaning. The VKD γ -carboxylation of the 5 essential VKD proteins in the liver and the 5 nonessential proteins in nonhepatic tissues sets up a dichotomy that takes advantage of the preferential distribution of dietary vitamin K1 to the liver to preserve coagulation function when vitamin K1 is limiting. Genetic loss of less critical VKD proteins, dietary vitamin K inadequacy, human polymorphisms or mutations, and vitamin K deficiency induced by chronic anticoagulant (warfarin/coumadin) therapy are all linked to age-associated conditions [30]: bone fragility after estrogen loss (osteocalcin); increased risk of type 2 diabetes (Gas6) [32]; arterial calcification (Mgp) [33, 34]; calcific aortic valve disease (periostin) [35]; increased chromosomal aberrations and spontaneous

cancer with mitotic spindle abnormalities (Tgfb1) [30, 36]. Studies on vitamin K deficiency as a cause of cancer are few but are suggestive [36, 37]. A triage perspective reinforces recommendations of some experts that much of the population and warfarin/coumadin patients may not receive sufficient vitamin K for optimal function of VKD proteins that are important to maintain long-term health [30].

2.2. DNA Damage and Cancer. Deficiency in each of the 7 micronutrients (iron, magnesium, zinc, and vitamins B6, C, folic acid, and biotin) that we have so far examined results in increased DNA damage in rodents, primary human cells in culture, or humans [24, 38–42]. Deficiency was severe in many of these studies, but further evidence discussed below suggests that modest levels of deficiency also can result in DNA damage and cancer.

Folate deficiency at moderate levels was the first micronutrient inadequacy to be clearly established as a mutagenic hazard for a considerable percentage of the US population. Low folate in mice was shown to cause chromosome breaks [43] and cancer [44]. Folate deficiency in human cells in culture was accompanied by chromosome breaks, cell cycle arrest in the S-phase, apoptosis, and high uracil incorporation into DNA, a likely cause of the breaks [38, 45–47]. A comparison of folate deficiency with radiation in breaking chromosomes has been done by us [38] and others [48, 49]. Folate deficiency in ex vivo human lymphocytes causes aneuploidy [50] and increased DNA oxidation and decreased DNA repair in rats [51]. Moderate deficiency of folate in humans (before folate supplementation of flour in the US) caused chromosome breaks at levels of deficiency present in 10% of the US population and in half of low income adolescents and elderly [47, 52, 53]. A study of human folate deficiency and micronuclei (chromosome breaks) [52] should have been the seminal paper in the nutrition-cancer field but has not been sufficiently appreciated. Micronuclei as a measure of chromosome breaks have been validated as a predictor of future human cancer [54]. In studies of Australian healthy adults, the third of the population with the lowest folate levels had a significantly increased level of chromosome breaks [55, 56]. Moderate folate deficiency has also been associated with human cancer, as reviewed in [51, 57, 58]. Moderate deficiency in B12 causes chromosome breaks in humans, apparently by the same mechanism as folate deficiency [53, 55].

Magnesium Deficiency. Magnesium intakes for ~56% of adults in the United States are below the Estimated Average Requirement (EAR), the current measure of micronutrient inadequacy (the RDA is set at 2 standard deviations above the EAR). Intakes below the EAR are especially prevalent among the poor, teenagers (78% of 14- to 18-year-old males and 91% of 14- to 18-year-old females), the obese, African Americans, and the elderly (81%) [31, 59–63]. Moderate magnesium deficiency causes genetic instability [64]. In humans, moderate magnesium deficiency has been associated with colorectal and other cancers [64–69], hypertension, stroke, osteoporosis, diabetes, and the metabolic syndrome [67, 70–72]. In a study of 4,035 men followed for 18 years, the highest quartile with serum magnesium at

baseline compared with the lowest had a 40% decrease in all-cause mortality and cardiovascular disease and a 50% decrease in cancer deaths [69]. In primary human cells in culture, magnesium deficiency leads to accelerated telomere shortening, activation of cell-cycle arrest proteins, premature senescence [41], and mitochondrial DNA damage (D. W. Killilea, B. N. A., unpublished observations). Magnesium deficiency in rats leads to chromosome breaks [73] and cancer [64]. In rats, a diet moderately deficient in magnesium increased mortality, blood pressure, inflammation, and oxidants and decreased resistance to oxidants compared with a standard or magnesium-supplemented diet [74]. This evidence suggests that supplementation programs should be considered because there is little risk of magnesium toxicity [70]. Good sources of magnesium are greens (magnesium is in the center of the chlorophyll molecule), whole grains, and nuts. A standard multivitamin-mineral (MVM) supplement does not contain sufficient magnesium (or calcium) because it would make the supplement too bulky.

Vitamin B6 deficiency, as measured by pyridoxal phosphate (PLP) levels in plasma, is associated with colorectal cancer; colorectal cancer decreased by 49% for every 100-pmol/mL increase in blood PLP level [75]. Serum levels of PLP were inversely associated with lung cancer in both smokers and nonsmokers in the EPIC study (100,000 person years) [76]. A significant inverse association between PLP level and gastric cancer has been shown in a large cohort study [77]. One possible mechanism is deficiency of B6 causing interference with heme biosynthesis causing release of mutagenic oxidants [24] though other mechanisms are also possible [78]. A sizeable percentage of the population not using supplements has inadequate PLP levels [79]; 49% of elderly women have inadequate (<EAR) B6 intake [31]. Low PLP levels are also associated with depression [80] and stroke [81].

Moderate deficiencies of calcium, niacin, vitamin E, retinol [56], or vitamins A, C, or E [82] are associated with chromosome damage. Severe deficiencies in rodents or human cell cultures for selenium, copper, niacin, choline, pantothenate, or riboflavin are also associated with chromosome breaks [24, 56]. Many of these and other moderate micronutrient deficiencies, when studied epidemiologically, are associated with cancer [24, 69, 83–93]. A number of human intervention studies with micronutrients report a decrease in DNA damage or cancer [52, 94–96] though more studies are needed to reach a definitive conclusion. The limitations of experimental approaches available for demonstrating a causal relation between micronutrient deficiency and cancer have been pointed out [97, 98]; a critical analysis of this large literature is not attempted here.

2.3. Mitochondrial Oxidant Release. A large literature, as discussed in Section 1, provides evidence that mitochondrial decay occurs with age and results in increased production of mutagenic oxidant byproducts of electron transport. To the extent that the DNA damage is caused by oxidants released from mitochondria, mtDNA will be damaged before nuclear DNA and should be more easily detected. Mitochondrial

decay appears to be a major contributor to both aging and its associated degenerative diseases, such as cancer and brain dysfunction, for example, complex I and Parkinson's disease, complex IV and Alzheimer's disease [24]. In mice, or human cells in culture, we found that severe deficiencies in zinc [42], iron [40], biotin [39], or vitamin B6 resulted in increased mitochondrial oxidative decay [24]. In all 4 cases, the mechanism could involve inhibition of heme synthesis which lowers levels of complex IV [24, 39], as discussed below.

2.4. Some Micronutrient Deficiencies Impair Heme Synthesis, Which Can Result in Oxidative Stress, Mitochondrial Decay, DNA Damage, and Cell Senescence. Seven micronutrients (biotin, pantothenate, pyridoxine, riboflavin, copper, iron, and zinc) are required for heme synthesis in mitochondria. A severe deficiency in any of these seven will cause a deficit of heme and therefore of complex IV, of which heme-a is an essential component [39, 99–103]. This mechanism is compatible with a triage response if complex IV is sensitive to modest deficiencies as well. The normal complement of complex IV keeps oxidants to a minimum; deficits of complex IV result in oxidant leakage, DNA damage, accelerated mitochondrial decay, and cellular aging [39, 99–103]. Deficiencies of iron, zinc, and biotin are discussed below.

Iron. Iron deficiency is the most common micronutrient deficiency in the world, and anemia is widespread in underdeveloped countries [104]. Iron intake in US menstruating women is low; ~16% are below the EAR, the standard measure of inadequacy [31]. Hispanic women and the obese are at greater risk of being iron deficient [105]. In humans, iron deficiency anemia is associated with poor cognitive development in toddlers [106–110], suggesting that iron deficiency in humans during critical periods of development harms the developing brain [107, 108, 111]. Severe iron deficiency causes loss of mitochondrial complex IV in selected regions in the brain of neonatal rats [112] as well as other changes in function, morphology, and physiology of the brain [107, 113]. Iron deficiency or excess in rats damages mitochondria and causes oxidant release, oxidative DNA damage, and decreased mitochondrial efficiency at levels both below and above the optimum [40].

Functional iron deficiency also is associated with diminished immune function and neuromuscular abnormalities [114, 115]. The effects of iron deficiency occur along a continuum [40, 107, 116]. Mitochondrial oxidant release resulting from nonsevere iron deficiency [40] could possibly be due to effects on heme-a biosynthesis [102, 103]. Iron deficiency without anemia can also occur in newborns exposed to intrauterine hypoxia, such as infants of preeclamptic or diabetic mothers [117]. In such cases, iron is prioritized to erythroid and hemoglobin synthesis, putting the nonerythroid tissues at risk of iron deficiency and hence heme deficiency [118, 119]. Dietary iron deficiency in the absence of anemia decreases aerobic capacity and physical work performance, which are improved by iron supplementation [120]. Iron deficiency has not been adequately

studied as a possible risk factor for cancer and the results are discordant [121, 122]. Many studies are looking for a monotonic relationship and do not take into account that one might expect cancer at levels of iron that are *both too low and too high* [40], as in hereditary hemochromatosis, a known risk factor for cancer [123]. Both iron deficiency and excess iron (excess iron may cause zinc or copper deficiency) in mice cause oxidant leakage from mitochondria, oxidative mtDNA damage, and mitochondrial dysfunction [40]. Iron accumulates with age and causes mitochondrial damage and early senescence in human cells in culture [124] and in rats [125]. Excess iron in human cells causes mitochondrial dysfunction, which can be ameliorated by ALC and LA [126].

Zinc. Zinc inadequacy is common in adults, ~12% of whom are below the EAR [31]. In human cells in culture, severe zinc deficiency causes complex IV deficiency and the release of oxidants, resulting in significant oxidative damage to DNA [42, 127, 128]. Zinc deficiency also causes chromosome breaks in rats [73] and is associated with cancer in both rodents and humans [129]. As discussed above, these observations reinforce the need to determine what degree of deficiency in humans results in DNA damage. We think it is likely that the trigger for decreased heme synthesis is the inactivation of the second enzyme of the pathway, δ -aminolevulinatase, which contains 8 atoms of zinc [102, 130]. Zinc deficiency in human cells also inactivates other zinc-containing proteins such as the tumor suppressor protein p53 and the DNA base excision repair enzyme, apyrimidinic/apurinic endonuclease, with a resulting synergistic effect on genetic damage [42, 127].

Biotin. Biotin deficiency is more common than previously thought; ~40% of pregnant women who do not take a multivitamin show metabolic signs of deficiency [131]. Marginal biotin deficiency is teratogenic in mice [131]. Biotin is a prosthetic group in 4 biotin-dependent carboxylases (3 of which are solely present in mitochondria) that replenish intermediates in the tricarboxylic acid cycle [132]. Biotin deficiency decreases the activity of these enzymes, leading to a decrease of 2 heme precursors, mitochondrial succinyl-CoA, and glycine, thus resulting in heme deficiency [39]. Biotin deficiency in normal human lung fibroblasts in culture caused a 40–50% decrease in heme content, oxidant release, premature senescence, and DNA damage [39]. The relationship of these effects to human intake amounts needs to be determined [133].

Despite the promise of decreasing mutation rates by optimizing metabolism, a cautionary note is that too much of some micronutrients, such as iron [40] or selenium [134, 135], as well as too little, can be harmful. Several micronutrients, for example, folate [58, 136, 137] or vitamin K [30, 138], may stimulate previously existing cancer cells. It should not be assumed that “too much of a good thing is wonderful.” Mae West, who said that, was not thinking about micronutrients.

3. Ameliorating Some Consequences of Mutation: Enzymes Lose Binding Affinity (Increased Km) for Coenzymes and Substrate with Mutation or Age

We reviewed [139] about 50 human genetic diseases due to defective enzymes, which were remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, thus partially restoring enzyme activity. Up to a quarter of mutations in a gene result in the corresponding enzyme having a decreased binding constant (increased Km) for a coenzyme resulting in a lower rate of reaction [139]. The review points out that many of the B vitamins, given at levels 10–100 times the RDA, can raise coenzyme activity levels by an order of magnitude or more, usually with minimal toxicity. Several single-nucleotide polymorphisms (SNPs) with a deleterious phenotype, under some conditions, decrease binding constants and thus may also be remediable by raising cellular concentrations of the cofactor by high-dose vitamin therapy. Our review raised the issue of whether some appreciable percentage of the population may require a higher level of a particular vitamin or substrate for optimum function.

A follow-up review [140] points out that it is common for proteins to become deformed with age, for example, membranes become stiffer by oxidation, deforming membrane proteins, and particularly in mitochondria. This raises the question of whether high dose B vitamins may be beneficial in the elderly. Deformation of an enzyme commonly decreases binding affinity (increased Km) for its coenzyme or substrate. Enzyme substrates and vitamin precursors of coenzymes can be elevated by feeding and may enhance the activity of a deformed enzyme. These observations also reinforce the importance of including age in dietary recommendations. For example, for vitamin B12, there is a special recommendation for the elderly based on their increased requirement, due to loss of uptake [141]. It also raises the question whether many metabolites, as well as vitamins, might be fed to improve functioning of enzymes in the elderly. The remediation of deformed enzymes, whether due to mutation or aging, is a field that shows promise and may be an inexpensive way to improve health.

The substrate binding affinities of complex I, III, and IV in mitochondria isolated from muscle of young and old mice were examined [142]. A kinetic analysis of complex III revealed a significant 29% age-associated increase in the Km (decreased binding) for ubiquinone-2. More recent work [143] reported a defect in the ubiquinone-binding site of cytochrome *b* in complex III in the interfibrillary mitochondria isolated from old rats [143]. The resulting defect in ubiquinone binding affinity is likely to increase superoxide production at this site. One possible mechanism of mitochondrial decay is that with age, stiffer membranes due to lipid oxidation or increased oxidative damage to mitochondrial proteins causes structural deformation of key enzymes such as carnitine acyl transferase that lowers their affinity for the enzyme substrate. Feeding old rats the substrate ALC with LA for a few weeks decreases

oxidative damage, allowing the synthesis of new carnitine acyl transferase with normal binding affinity (Km) [9]. This partially restores mitochondrial function, decreases oxidants, neuronal RNA oxidation, and mutagenic aldehydes, and increases rat ambulatory activity and cognition [6–9]. Mitochondrial complexes were examined [144] in the brain of young and old rats, with and without dietary ALC and LA. ALC and LA partially restored function of complex I to the level of the young, but by restoring Vmax, not Km for CoQ and NADH [144]. Increased levels of CoQ and niacin might overcome the increased Km. The Km mechanism for restoring function is not the only possible one; decreased oxidants may increase protein activity by increasing stability as well [6, 9, 144]. ALC and LA are not micronutrients, as they are made in the mitochondria, but they are illustrative of many normal metabolites that may be useful in the elderly.

4. Conclusion

The work on acetyl carnitine and lipoic acid suggests that decay of mitochondria leading to cancer and a variety of other diseases of aging is not inevitable but can be delayed by various interventions to improve metabolism. Understanding the mechanisms will suggest still other interventions. For example, if the effectiveness of lipoic acid is because it induces the ~200 enzymes in the phase-2 defense system against oxidants, as seems likely, then the whole area of optimizing our various inducible defense systems for longevity by hormetic mechanisms becomes attractive and we are at the start of the discovery of many interventions.

If the triage hypothesis proves to be correct, as the vitamin K analysis suggests, it will demonstrate the importance for a long and healthy life of avoiding modest micronutrient deficiencies for minimizing cancer and other age-related diseases, and for changing how people think about nutrition and health. Most of the world's population, including that of the US, is inadequate in one or more micronutrients according to current intake recommendations. Yet, because there is no overt pathology associated with these levels of deficiency, there has been little public concern. The triage hypothesis framework may facilitate the discovery of sensitive and specific biomarkers of micronutrient insufficiencies that can be used to optimize metabolism at a personal and population level. Current recommendations do not take into account the insidious biochemical consequences of metabolic triage. We think that we can show that insidious damage is indeed occurring at modest levels of deficiency and that this damage will increase the risk of cancer, cardiovascular disease, cognitive dysfunction, and the other diseases associated with aging.

The genomic variability between individuals is being explored at a rapid rate, but a correct understanding as to how to intervene awaits bringing nutrition, particularly micronutrient-dependent proteins into the picture. We believe that the analysis of binding constants is the beginning of a large field that will make it possible to overcome a large class of deleterious genetic changes by nutritional interventions.

Various lines of evidence reviewed here suggest that healthier lives are to be gained by optimizing our metabolism. More attention to balanced diets and optimizing micronutrient intake could have a major effect on delaying the degenerative diseases of aging. My vision is that this will be done in the future by individuals measuring their own levels of micronutrients from a finger prick of blood in a machine in their local pharmacy (<http://www.reliadiagnostics.com/>), and tuning up their metabolism by adjusting diet or taking supplements—the beginning of an age of true preventive medicine.

Conflict of Interest

Dr. Ames is one of the founders of Juvenon (<http://juvenon.com/>), a company that has licensed the University of California patent on acetyl carnitine + lipoic acid for rejuvenating old mitochondria (Ames and T. Hagen, inventors), sells acetyl carnitine + lipoic acid supplements, and does clinical trials on them. Ames founder's stock was put in a nonprofit foundation at the founding in 1999. He is director of Juvenon's Scientific Advisory Board, but reimbursement for that from Juvenon is given to the foundation.

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