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These pictures show Alan Sinclair's Mobile Perfusion Unit, which paid its first visit to Cornwall for the 2002 Cornwall Cryonics Conference on 7/8 September, 2002.

For a full report of this conference, please see http://www.cryonics-europe.org

Special Extended Issue

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The Role of Enzymic Cofactors in Aging
or
How to Live to 200

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Overview

This monograph is about living long and healthily with supplementary B-vitamins and minerals. It explores the relationship between aging and the enzymic cofactors, derived from dietary B-vitamins and minerals. The hypothesis explored here is that many of the degenerative aspects of aging are due, in part, to dietary enzymic cofactor deficiencies and their consequent metabolic dysfunctions. These aging-associated metabolic dysfunctions are partially correctable with dietary supplements of the B-vitamins and minerals, meriting the description of anti-aging micronutrients.

Introduction

To live longer we know we should cut down on tobacco, alcohol and calories, drink water[75] and drive carefully. Less well known are the benefits of various micronutrients in our diet: micronutrients such as the B-vitamins, minerals and other dietary precursors to enzymic cofactors; yet the health and longevity benefits of the B-vitamins and minerals are much greater than the more heavily publicised anti-oxidants, such as vitamins C and E. We survey the dietary cofactors that have extended lifespan in animals, by slowing aging [1-6]. We examine the experimental methodology used and their relevance to, and implications for, humans. We examine a number of theories of aging in relation to various dietary-derived enzymic cofactors. In the light of this hypothesis we look to see what other dietary micronutrients may slow aging, or at least improve health. Finally we examine some prevalent misconceptions about vitamins.

Anti-Aging Enzymic Cofactors

Any anti-aging micronutrient will extend lifespan, by definition, but life span experiments on humans will only be completed long after we are dead, so we must, in the meantime, look to animal lifespan experiments for guidance. Raising the dietary levels of cofactor precursors does indeed extend lifespan in a range of animals[1-6], suggesting that the dietary cofactor precursors are anti-aging micronutrients. Most longevity experiments on mammals are done on rodents (rats or mice); lifespan experiments on insects tend to be done on fruit flies. In each case, to qualify here as anti-aging, the life-extending cofactors have to have been tested against a control group of animals receiving a normal diet, comparable to our modern diet. That is to say, the control diet was already sufficiently enriched to prevent any frank or overt vitamin or mineral deficiency diseases.

The following table lists the anti-aging effects on lifespan of some dietary cofactors,

Anti-Aging Micronutrients	Mean average lifespan increase in fruit flies	Mean (Max) lifespan increase in rodents
Niacinamide (vitamin B_3)	15% [4]	
Pantothenate (vitamin B_5)	27.8% [1]	19.5% [3]
Pyridoxine (vitamin B_6)	10.5% [1]	>11% [6]
Biotin (vitamin B_7)	0% [1]	
RNA	11.3% [1]	16% (8-16%)[2b]
B_6 + B_7 + RNA	20.3% [1]	
B_5 + B_6 + B_7 + RNA	46.6% [1]	
Chromium picolinate		27% (17%) [5a-e]

g = gram, mg = milligram, ug = microgram

Note: Empty cells indicate no data available, not a zero or a null result. Maximum lifespan data in brackets, ():

Let's interpret the results presented in the anti-aging table:

Lifespan: Mean & Maximum

As a measure of lifespan extension I have used the mean average and maximum lifespan of the experimental animals (or cohort), relative to the controls, known as the cohort mean and maximum lifespan.

Cohort maximum lifespans – if measured by the age of the last survivor - are subject to high random scatter or uncertainty, since only one animal defines the maximum age from a relatively small group. A better measure of maximum lifespan is the mean average lifespan of the longest-lived 10% of the cohort.

The ideal anti-aging intervention would increase mean lifespan ("squaring" the survival curve, generally interpreted as a sign of improving health) more than maximum lifespan (extending the survival curve, generally interpreted as a sign of retarding the aging process). Unfortunately maximum lifespan data are less frequently reported than mean average lifespan data. In the absence of definitive maximum lifespan data for a micronutrient we can only extrapolate from other micronutrients with reported mean and maximum lifespan data, where the maximum/mean lifespan extensions ratios are remarkably similar at 63%.[5, 7]. Any micronutrient with a preventative action across a broad range of degenerative diseases, e.g. neurological decline, cancer and cardiovascular disease, and which also extends mean lifespan, I would expect to extend maximum lifespan: i.e. have an anti-aging effect. I would exclude any micronutrient from being anti-aging if it only acted across a limited range of degenerative diseases. All the above micronutrients qualify as anti-aging by these criteria.

Animal Models

Rodents and fruit flies are very dissimilar creatures, with their last common ancestor living prior to the Cambrian Explosion, about 670 million years ago[30], yet, despite this, mammals and insects share most of the same fundamental metabolic pathways, including their dependency on the same basic B-vitamin-derived coenzymes[84a, 84b]. Only the plants and some single-celled organisms (e.g. prokaryotes, including bacteria) can synthesise these coenzymes from scratch. All animal life, from insects to mammals, depends on life lower down in the food chain to source their B-vitamins and derivative coenzymes; all animals share the same dietary dependency upon B-vitamins[84a, 84b]. This is not true for some of the other vitamins, for instance vitamin C, for which substantial differences exist in the synthesis of, and requirement for, between different branches of animal kingdom.

Comparing the life extension percentages for the rodents and fruit flies, for which we have comparable data (i.e. for vitamins B_5 (pantothenate), B_6 (pyridoxine) and dietary RNA) we find they are within approximately 40% of each other. This is remarkably good agreement, considering the lifespan differences between the fruit-flies and rodents; the anti-aging action of these enzymic cofactors must operate at a very basic level, common to all animals, and should extrapolate very well within mammals[80], from rodents onto humans, with perhaps only a 6% intrinsic error, since humans are approximately 7 times more closely related to rodents than fruit flies[31]. Calorie restriction, another anti-aging intervention, extends the maximum lifespans of rodents and fruit flies by approximately the same factor[33], which, again, suggests that the basic aging mechanisms in all animals are similar.

The health benefits to already healthy humans of supra-RDA levels of micronutrients - as demonstrated by many placebo-controlled trials[47-61] and epidemiological studies[11-14], a view finally endorsed in a JAMA review[82] - are further circumstantial evidence that their anti-aging effect will extrapolate onto humans.

Synergy

The life-extending, anti-aging effect of the enzymic cofactors from dietary RNA, B_5 (pantothenate) & B_6 (pyridoxine), in combination on insects, is approximately the sum of the effects separately[1b], presumably because the enzymic cofactors can't substitute for each other; each enzymic cofactor facilitates its own distinct metabolic action, independently of the other enzymic cofactors. We've already noted the apparent commonality of the operation of these enzymic cofactors on all animals; we expect their anti-aging nature to synergistically[119] extrapolate from insects on to rodents and humans.

This postulated anti-aging synergy between enzymic cofactors, in mammals, is rendered still more plausible by the health synergy between various combinations of the vitamins B_1 (thiamine)[110d], B_2 (riboflavin)[100, 110a-d, 113, 114], B_3 (niacinamide)[43c, 55a, 113, 110d], B_5 (pantothenate)[112], B_6 (pyridoxine)[11b, 43a-d, 52c, 86a, 86b, 110b-d, 113, 114], B_7 (biotin)[37d, 55d], B_9 (folate)[11b, 43a, 43b, 43d, 52a-c, 53], B_{12} (cobalamin)[11b, 43a, 43c, 52a, 52b, 53, 112], C[13, 100, 110d], D[100] & E[13], enzymic cofactors acetyl-L-carnitine[37a-d], alpha lipoic acid[37a-c] and the minerals chromium[55a, 55d], zinc[110a, 110b], selenium[45], calcium[100] and magnesium[45, 86a, 86b].

Adding up the mean average life extension percentages from B_3 (niacinamide), B_5 (pantothenate), B_6 (pyridoxine), RNA & chromium we get an approximate 85% mean lifespan extension. Taken at face value, it implies that human mean average life spans of over 130 years are achievable, by dietary intervention alone, almost doubling mean average lifespan.

The two definite maximum lifespan extensions[5, 7] are both approximately 63% of their mean lifespan extensions; the whole combination yields the expectation of a 54% maximum lifespan increase; an extension of a maximum lifespan in humans from 122 years to almost 187 years.

Theories of Aging

Developmental or programmed theories of aging used to be popular, in which growing old was regarded as similar to growing up, controlled by biological switches and hormones. Gerontologists used to search for "death hormones" and experimented with monkey-gland transplants, and such like, in a doomed attempts at rejuvenation. But if ageing were a developmental process then we'd expect to see some aging-arrested individuals (immortals), just as we see developmentally-arrested individuals[94]. Later "rates of living" theories were formulated, where lifespan was limited by total lifetime metabolic expenditure or number of heartbeats. These attempts have all failed[28a].

With an increasing awareness of evolution and the "selfish gene" concept[28b], aging came to be regarded as a side-effect of evolution's focus on our genes, with our bodies (soma) acting as disposable genetic transmitters or conveyers of the germ line to the next generation. According to the "disposable soma" theory of aging[28c], aging is a simply a reflection of the low priority evolution assigns to our individual survival after we have successfully reproduced. Evolution hasn't programmed us to grow old and die, it is just a side effect of not being perfectly constructed for individual immortality. Evolution has designed us with enough built-in redundancy and repair mechanisms to see us past reproduction and child rearing, after which we decline, not through design or malice, but simply by evolutionary indifference; there is no master aging switch; aging is a multifactorial process, with no single cause. No single mechanism, such as telomeres, loss of redundancy, mitochondrial dysfunction, genetic degradation, glycation, free-radical damage is going to be the complete answer. Rather, during aging all the above factors, plus a lot more we can't even guess at, at the moment, degrade all aspects of our metabolism, in a vicious circle, a downward spiral towards complete homoeostatic breakdown, called death.

The hypothesis advanced here is that aging is largely the progressive breakdown of metabolic homeostasis, coupled with the erosion of built-in redundancies (of various forms), for a variety of reasons, known and unknown. Enhancing the performance of our enzymic control systems may delay this downward spiral. Enzymes depend critically on the presence of coenzymes and other enzymic cofactors (see Glossary and Appendix A for details). Correcting various enzymic cofactor deficiencies may slow this metabolic degradation, improve our health and prolong life.

We shall now examine some of the postulated causes of aging and see how they relate to the various dietary enzymic cofactors.

Methylation

Methylation[19], the transfer of methyl groups (CH_3) in metabolic reactions, is vital for many aspects of life. All methylation is effected by the coenzyme, SAMe, with the exception of the methylation reaction that regenerates SAMe itself from homocysteine via methionine which requires methylcobalamin. Optimal methylation is essential for preventing neurological decline, cancer and cardiovascular disease.

Methylation protects against the DNA transcription errors during cell division[25a, 25b, 18]. Every time a cell divides errors may creep into the daughter cells' DNA, leading, eventually, to cancer, which is why body tissues subject to a lot of cell replication (such as the lining of the colon) are prone to develop cancer; errors (mutations) are introduced into the DNA by the associated DNA copying process. Long-term folate supplementation is particularly effective against colon cancer in humans[11a, 11b, 41e]. Breast cancer, which is caused by hormonally triggered cell division, has a reduced incidence in high-folate consumers[97a, 97b]. If the protective effect of folate is due, as hypothesised, to reducing the DNA transcription errors and maintaining genomic stability[18] then it should also be effective, to some degree, against most cancers[17], and would nicely compliment the DNA repair effect boosted by NAD, a vitamin B_3 (niacinamide) derivative (see section on Nuclear DNA).

SAMe production is sensitive to dietary intakes of B_9 (folate), B_6 (pyridoxine) and B_{12} (cobalamin)[11a, 25, 18], and, for some people, B_2 (riboflavin).[115a, 155b] Maintaining high levels of SAMe keeps homocysteine levels low which, in turn, is critical for maintaining cardiovascular health[19].

Summary: Ensuing adequate methylation, with the B vitamins B_6 (pyridoxine), B_9 (folate) and B_{12} (cobalamin), protects against a range of age-related disorders, in particular cardiovascular disease and some cancers, and can be regarded as being anti-aging.

Beyond Methylation; the Enzymic Cofactor Hypothesis

Methylation is just one of the many vital metabolic transformations mediated by coenzymes, in this case the coenzyme SAMe. Some of the other coenzyme mediated transfer reactions (see Appendix A) include acylation, carboxylation, glycosylation and oxidation-reduction reactions involving both 1- and 2-electron transfers in both the aqueous and lipid soluble cellular compartments.

Amongst all the coenzyme mediated transfer reactions available there is no reason to suppose that methylation occupies a privileged role. Enhancing methylation is believed to slow aging, delaying the onset of degenerative disorders[19]; perhaps enhancing the other coenzyme-mediated reactions would be similarly beneficial to fighting aging. This is this monograph's aging and enzymic cofactor hypothesis. Methylation is an example of a one particular aspect of the broader coenzyme or enzymic cofactor hypothesis; many of the degenerative aspects of aging are due, in part, to dietary enzymic cofactor deficiencies and their consequent metabolic dysfunctions. Most of the body's coenzymes are sourced from dietary RNA and the B-vitamins; these micronutrients are vital in maintaining metabolic homeostasis, optimum function and slowing aging. Minerals supply additional enzymic cofactors.

In the previous section on methylation we assumed that the cardiovascular and anti-carcinogenic health benefits of the B-vitamins B_6 (pyridoxine), B_9 (folate) & B_{12} (cobalamin) were due to their methylation-enhancing properties. But it is equally likely, at the very least, that the coenzyme optimising activities of these three B-vitamins are methylation-independent. For instance, the low levels of the same three B-vitamins are associated with Alzheimer's dementia,[41a-h] independently of their methylation-related and homocysteine-lowering effect.[79a, 79b] Intervention trials with B_1 (thiamine)[106a-c], B_9 (folate) [107], B_{12} (cobalamin)[104a-e] , acetyl-L-carnitine[105a-g] (precursor to coenzyme carnitine) and alpha lipoic acid[98] (precursor to coenzyme lipoamide) have all shown success, to varying degrees, in stabilising the progression (and presumably prevention also) of Alzheimer's and other forms of dementia[106d]. In general benefit is greatest with early intervention[104b, 104c, 107] and in young subjects[105f, 105g].

Summary: As with methylation, it is likely that the many other reactions mediated by coenzymes, mostly derived from dietary RNA, B-vitamins and minerals, will be critical for metabolic homeostasis, slowing aging and maintaining health.

Dietary Nucleic Acid (RNA)

Using the aging and enzymic cofactor hypothesis we can explain the benefit of dietary RNA. During digestion RNA is broken down into, and absorbed as, nucleotides and nucleosides. Nucleotides and nucleosides have a direct metabolic action, independent of their role in RNA, and are precursors to a number of coenzymes. The energy-supplying coenzyme ATP is a nucleotide, for instance, critical to our metabolism. There are other nucleotide

coenzymes, such as UDP and CDP, required for biosynthesis of glycosaminoglycans, lipids and glycogen. (NAD and CoA are also nucleotide coenzymes, but are not derived from dietary nucleic acids.) Ribozymes, enzymes constructed from nucleotides instead of amino acids, are another example of the role of nucleotides.

RNA has a high turnover, being required for all gene expression and protein synthesis. We are capable of synthesising nucleotides from scratch (via the de novo pathways) but this is very expensive, in terms of the energy required. To ease the burden of de novo synthesis we have evolved the so-called salvage pathways which process nucleotides & nucleosides available both from our diet and from the natural turnover and breakdown of cellular RNA.

The amount of RNA in foodstuffs varies widely. Sardines, one of the most RNA rich foods, are between 0.5% – 1% by weight. To ingest the 250mg of RNA required for the life extension effect, we need only eat 12 – 25 g of sardines per day.

Summary: RNA enriched diets are beneficial to health, and in particular the immune system[24, 26a, 26b, 60, 61], and have extended lifespan[1, 2].

Free-Radicals / Antioxidants

The free-radical theory of aging was started in the 1950s and popularised in the 1970s & 1980s[109]. Free-radicals possess unpaired electrons, bonding with neighbouring molecules in an uncontrolled fashion, causing permanent unwanted bonds between molecules (cross-links) and damaging DNA. Many metabolic reactions produce free-radicals, particularly oxidation-reduction reactions. Free-radicals probably contribute to aging, but the extent of their contribution is debatable. Attempts to demonstrate the life-extension properties of vitamin C & E, given singly, have failed, although they do seem to improve cardiovascular health and, to a lesser extent prevent cancer, lowering age-related mortality rates when taken in combination[13, 14].

Antioxidants are substances that mop up the free-radicals. Vitamins C & E are antioxidants. The B-vitamins and minerals are not antioxidants, although they can produce an antioxidant effect by boosting the action of our antioxidant enzymes. Some of our antioxidant enzymes are catalase (which break down hydrogen peroxide, H_2O_2 to H_2O and O_2) & glutathione peroxidase (converts hydroperoxide, R-O-OH to ROH), superoxide dismutase (which combines the superoxide radical, O_2- with H+ to form H_2O_2 and O_2). Any enzymic cofactors that boost the activity of these enzymes have an indirect antioxidant effect. Zinc, copper and manganese, for instance, are required for the various forms of superoxide dismutase. Zinc supplements reduce post exercise free-radical activity[90]. Vitamin B_6 (pyridoxine) is required for the synthesis of all enzymes, anti-oxidant or not, and other proteins.

Selenium is required for the production of the antioxidant enzyme glutathione peroxidase. Supplementation with selenium has shown remarkable benefits in reducing cancer rates[72] and overall mortality. Trials on humans with 200ug/d for just 5 years halved the cancer mortality and reduced over-all mortality[15]. Other human epidemiological studies, which show lower rates of cancer and cardiovascular disease in areas and countries with high selenium intake, suggest that zero cancer incidences may be achievable at approximately 400ug/d[16]. It's worth noting that it is very hard to get this amount from a diet – supplements may be safer since the dosage is easier to control. Part of the reason why selenium deficiency is so common is that selenium, like chromium, is only minimally required by plants[23b]; plants can thrive in selenium poor soils, leading to selenium poor diets. Brazil nuts, for instance, which are popular as a dietary source of selenium, may vary by a factor of 10,000 or so in their selenium content[23a], which, considering that a few milligrams may be toxic[72a, 73], means that you risk either deficiency or overdosing by relying on diet alone as a source of selenium.

Free-radicals, although injurious to health, may not be involved in aging. The selenium trial[15], which halved cancer mortality, did not reduce other causes of death. This suggests that free-radicals, or at least hydroperoxide ions, whilst they contribute to cancer, do not contribute to aging. And indeed, one animal experiment[33a] confirms that whilst selenium improves the survival curve it does not extend it, i.e. cohort mean average lifespan was extended, but not maximum lifespan. This is what we might expect from a nutrient with a limited, though effective, range of action, as previously discussed. Additionally, elevated levels of the antioxidant enzyme superoxide dismutase failed to extend

lifespan in mice[92]. On the other hand curcumin[7], an antioxidant with anti-carcinogenic properties, has extended maximum as well as mean lifespan, although this may to due to curcumin's non-antioxidant behaviour.

Oxidative damage and free-radicals, whilst not implicated strongly in aging, are causative for a number of degenerative conditions, such as lipofuscin accumulation, in post-mitotic cells. Vitamin E, a free-radical scavenger, is effective[116a-c] against lipofuscin accumulation, which may be reversible[116c, 166d]. Any anti-oxidant strategy would be expected to slow the progression of this and other oxidative-induced conditions; micronutrients such as vitamin B_6 (pyridoxine)[166e] and the minerals selenium (and perhaps zinc and curcumin) should be helpful.

Summary: Vitamin B_6 (pyridoxine) and E and the minerals selenium and zinc (and perhaps copper, manganese and curcumin) are important for optimal antioxidant enzyme function, although the role of antioxidants in aging is unclear.

Glycation

Glycation refers to the non-enzymic binding of glucose to other molecules. This binding is uncontrolled and destructive, causing the faster aging exhibited by diabetics, and, since as we age we all tend to become pre-diabetic (with reduced glucose tolerance, rising insulin and glucose levels), it is implicated in normal aging[83a-h].

Chromium, one of the anti-aging minerals, is implicated in glycation. Animals fed chromium picolinate have lower fasting glucose and insulin levels and improved glucose tolerance. Chromium is a cofactor for insulin function in animals, the only known physiologic role of chromium. A range of studies on pigs, dogs and rodents suggest that insulin function is optimised when the chromium intake in ug is above 1/5 of the number of calories consumed[5d]. In humans, chromium and chromium picolinate benefits both the healthy[55a-c] and adult-onset diabetics[10a-c] lowering insulin levels, fasting glucose levels and improving glucose tolerance. Both vitamins B_3 (niacinamide)[55a] and high-dose B_7 (biotin)[55d] synergise with chromium in improving insulin-resistance.

Independently of any synergy with chromium, vitamins B_1 (thiamine)[88c-e], B_3 (niacinamide)[85], B_6 (pyridoxine)[88a-e], and B_7 (biotin)[93] along with minerals magnesium, zinc[91], in doses greater than the RDA, improve insulin-resistance and lower glycation levels.

Calorie restriction (see later) also lowers glycation and extends lifespan, but whether it will synergise with the above micronutrients is unknown.

Summary: chromium, magnesium and zinc, along with vitamins B_1 (thiamine), B_3 (niacinamide), B_6 (pyridoxine) and B_7 (biotin), are effective in preventing or ameliorating diabetes and reducing glycation levels, slowing aging.

Telomeres

Telomeres are repeating sequences of DNA at the end of chromosomes. In humans, but not all animals, as cells divide their telomeres shorten, which is why children have longer telomeres, on average, than adults. Eventually, after sufficient cell divisions, as telomeres become too short the cells reach the Hayflick[63b] limit, cease dividing (replicative senescence) or even die (apoptosis)[63a]. Some of our tissues, e.g. skin, bone marrow and gut, which require constant cell division, express an enzyme, telomerase (an example of a ribozyme), which lengthens telomeres, enabling constant tissue proliferation throughout life. Telomerase expression is usually switched on in cancer cells; inappropriate over-expression of telomerase being one of the critical mutations a cancer cell requires to replicate unchecked.

Telomere length represents the trade-off between tumour-suppression and tissue-repair[62c]. Short telomeres enhance tumour suppression, but with an earlier replicative senescence shutdown at a reduced Hayflick limit. Long telomeres allow more extensive and later tissue proliferation, along with greater reproductive time-spans, but with an increased risk of tumours.

One of the theories of aging is that telomere shortening drives the aging process, by limiting the number of cell divisions available for tissue repair. On one hand p53 over-expression (a gene which telomeres use to induce replicative senescence or apoptosis) accelerates the appearance of aging and shortens longevity[64a, 64b]. On the other hand telomeres don't shorten in rodents[62d], yet rodents seem to age in the same way as humans, albeit faster. Also, amongst mouse strains, there is no correlation between lifespan and telomere length[62a]. Finally, amongst primates, humans have the longest lifespans, yet the shortest telomeres[62b]. So, again, it seems unlikely that telomeres directly determine lifespan. It is more likely that telomeres primarily function to protect us from cancer. Amongst the primates, perhaps our short telomeres reflect the higher level of anti-cancer protection required for longer-lived humans?

Another factor to consider is that telomere shortening may not be driven just by cell division. There is some evidence that telomeres pick up damage all the time[63c-e], hastening their shortening, independently of cell division; reducing and combating cellular stress, by maintaining adequate coenzyme levels, will not only slow the rate of cell division (through lowering the requirement for damaged tissue repair and proliferation) but may actually extend the number of cell divisions permitted before the Hayflick limit is reached. Either way, by looking after our health, we can slow telomeric shortening and extend our tissue's regenerative potential[63f].

Summary: the role of telomeres in aging is unclear.

Nuclear DNA: Damage and Repair

As we age our DNA degrades. Since our DNA encodes genes for the structures of all our proteins, including enzymes, maintaining genomic stability is critical for staving off age-related degradation.[95a-c] Radiation, free-radicals, glycation and our own imperfect DNA copying mechanisms, all contribute to DNA damage (mutations) building up, chromosomal breaks, gene mal-expression, expression of defective proteins, including malfunctioning enzymes. As with all aspects of aging, it is difficult to separate cause and effect. Is DNA damage the cause of aging or just an effect? Probably both, since animals exposed to radiation, which induces DNA damage, show signs of accelerated aging, in addition getting more cancer.

DNA is a double stranded molecule, with the genetic information duplicated on both strands. If the damage is confined to one of the strands then it can be repaired by the base excision-repair mechanisms. Enzymes remove the damaged sections of DNA from one strand (excision) and then rebuild (repair) the lost sections of the strand, using the other strand as a template. One of the enzymes involved in this generalised DNA excision repair process is poly(ADP-ribose) polymerase, or PARP, which produces a repeating poly(ADP-ribose) polymer sequence. PARP requires nicotinamide adenine dinucleotide (NAD) as a substrate, and is very sensitive to NAD concentrations, as shown by an experiment in which rodents exhibit increased resistance to UV-induced cancer when fed a diet rich in vitamin B_3 (niacinamide), which elevated cellular NAD levels by a factor of 3 or so[27c]. Vitamin B_3 (niacinamide) is a precursor to the coenzymes NAD and NAD-phosphate (NADP). Although not strictly a vitamin - our bodies can produce NAD/NADP from dietary tryptophan - it functions like one since this production is not very efficient. Dietary consumption of niacin elevates NAD tissue concentration, in animals and humans[27d, 27e], which up-regulates the activity of PARP, increasing the DNA repair efficiency and reducing the induced[27c, 27f] cancer rate. Similar behaviour is expected in humans[27d], who are typically more NAD deficient than many animals.

Magnesium ions are essential for the operation of kinases, enzymes that use a magnesium-ATP complex as a phosphoryl-group donating substrate, and are critical in maintaining genomic stability[38d]. Magnesium deficient animals show signs of premature aging[38b-d]. In humans magnesium has been successfully used to treat kidney stones, high blood pressure, migraine, coronary artery spasm, irregular heart rhythms and diabetes. Levels of magnesium in drinking water correlates with longevity via decreased cardiovascular disease[38a]. Most people are magnesium deficient; their diets don't even supply the RDA of magnesium; it seems sensible to supplement with magnesium to stave off premature aging. Magnesium synergises well with vitamin B_6 (pyridoxine).[86a, 86b]

The ability of selenium[15, 16, 72] to reduce cancer incidence suggests the selenoenzymes provide some genomic protection.

Summary: Vitamin B_3 (niacinamide), the NAD precursor, can provide considerable protection against DNA damage generally. Since almost all adult cancers are the result of DNA damage then this may prevent many cancers. Magnesium and selenium are also be important for genomic stability. If DNA damage is implicated in aging then magnesium and vitamin B_3 (niacinamide) may be essential to help ward off premature aging.

Mitochondrial Dysfunction

Our cells have two centres of DNA, the nucleus and the mitochondria. Experiments with fruit flies suggest that the mitochondrial DNA is more important than nuclear DNA in aging[46]

Mitochondria are sub-cellular organelles possessed by all nucleated cells. The mitochondria multiply independently of their host cell and possess their own DNA. Once upon a time, perhaps a billion or so years ago, the mitochondrial ancestors were independent free-swimming organisms that evolved the unique ability to process oxygen to generate bio-energy, which we call respiration. Some of them formed a productive symbiotic relationship with other cellular life, where, today, the mitochondria act as powerhouses to their hosts. The extra energy available to these symbiotics enabled them to go on to form all the complex multicellular organisms, such as animals, plants and fungi. (The ancestor of all plants subsequently acquired chloroplasts for photosynthesis, in a similar fashion.) Unfortunately respiration of oxygen also produces free-radicals (or in this context reactive oxygen species or ROS), which are harmful. As we age our mitochondrial DNA degrades, presumably due to ROS-induced damage, and the efficiency of the mitochondria decline. Experiments with fruitflies have shown that longevity is transmitted by the mitochondrial DNA (which is inherited maternally) and correlates negatively with ROS production[46].

Transport of the respiratory substrates into the mitochondria requires the enzyme carnitine acyltransferase, I & II, which, in turn, requires carnitine. Feeding old rats with diets rich in carnitine and/or alpha-lipoic acid (a coenzyme pre-cursor) reversed many aspects of age-related mitochondrial decline[37a, 37b], including lowering ROS production[37c], although lifespan results are not yet available. The benefits of carnitine may synergise with biotin[37d].

Many other coenzymes are involved in mitochondrial metabolism. Feeding fruitflies vitamin B_3 (nicotinamide) lowered ROS production and extended their lifespans[4].

Summary: Carnitine, vitamin B_3 (niacinamide) and alpha-lipoic acid are effective at maintaining or even rejuvenating mitochondrial function. Early lifespan results with B_3 are promising[4].

Redundancy versus Regeneration

Reliability theory[87], originally an engineering concept, basically says any complex system requires redundancy in its irreplaceable elements. Evolution has given us both an imperfect set of repair mechanisms and some redundancy, in differing amounts in our various sub-systems and organs, as the most cost-effective way of prolonging our lives, according to the dictates of disposable soma. The marginal cost of the extra redundancy is balanced by the extra cost involved in developing more efficient repair mechanisms. This is a trade-off. Organs that regenerate very well (e.g. liver) have no need for redundant spare capacity, whereas organs that regenerate very poorly (e.g. kidneys and brain) are designed with lots of spare capacity.

Our kidneys are largely irreplaceable due to having almost no regenerative capacity. To compensate evolution gives a large amount of back-up, spare capacity, so that in our youth between 75%-90% of our kidneys function is redundant. If we live long enough, chronic renal failure will eventually kill us, progressive damage being inflicted by glycation and vascular dysfunction, amongst other causes. The earlier in life anti-glycation and vascular protective measures are started, such as extra dietary chromium[10, 55a-c] and vitamins B_3 (niacinamide)[55a], B_6 (pyridoxine)[19, 88], B_7 (biotin)[55d], B_9 (folate)[19] and B_{12} (cobalamin)[19] the longer our renal redundancy will last.

Some regions of our brains have a similar degree of redundancy. Parkinson's disease is characterised by massive degeneration and loss (up to 98%[177g]) of dopaminergic substantia nigral neurons[177h]. This loss is at least partially driven by oxidative damage and can be slowed by anti-oxidant intervention. Anti-oxidants demonstrated to slow the progression of Parkinson's include melatonin [117a, 177b], vitamin D_3[117e] and E[117d], and flavonoids[177f] with a high

probability that alpha lipoic acid and carnitine would provide additional mitochondrial support[37a, 37b, 177c] along with other anti-oxidant micronutrients such as vitamin B_6 (pyridoxine) and the mineral selenium (and perhaps zinc and curcumin). Anti-glycation measures, with vitamin B_6 (again), chromium, and B_7 (biotin) may also slow the progression of Parkinson's.

Another type of redundancy is our genetic redundancy against cancer. Genetic damage is at the root of almost all adult cancers[17] - a cancerous cell being the end product of a chain of approximately 5 independent mutations[9]. This represents genetic redundancy against cancer, which we erode every time one of the critical pre-cancerous genes is damaged and not repaired. The effects of stopping smoking neatly illustrate the difference between regenerative and redundant components. A smoker has an increased risk (relative to a non-smoker) of the two main killers of old age: cardiovascular disease (stroke, heart attack) and cancer. Within a few years of stopping smoking the ex-smoker's cardiovascular risk is pretty much the same as if they had never smoked. The risk of cancer, though, always remains elevated[78]; the cardiovascular system is capable of rejuvenation, whereas our genome is not. But irreversible genetic damage or mutations accumulate at a fairly steady rate past the age of 20 years[9]. As we age we irreversibly lose the genetic redundancy we are born with. Eventually cells turn cancerous, as we have seen. This suggests that we can rejuvenate our cardiovascular system by taking micronutrients, but that we but we can only retard further damage and deterioration to our genome, not reverse it. Genomic protection strategies, such as vitamins B_3 (niacinamide) [27c, 27d, 27f, 72d], B_6 (pyridoxine)[11b, 19], B_9 (folate) [11a, 11b, 18, 25a, 25b, 53], B_{12} (cobalamin)[11b, 18, 41e, 53], selenium[72a-d] and magnesium[38b-d], need to be implemented whilst we are still young for maximum, long-term, protective effect.

In all cases, though, intervention strategies can only slow the irreplaceable loss of redundant spare capacity. The earlier any interventions are started the longer the redundancy will sustain us. This is almost certainly why the life-extension effect of supplements is diminished the later in life they are started. With dietary RNA[2a], for example, when the supplementation was started in old age (approximately equivalent to 60 human years) then there was a 9% mean life extension, as measured against the controls' total mean life span, whereas for the whole-life supplemented mice there was a 16% mean life extension. This suggests that extra dietary RNA not only retarded but also actually reversed some of the aspects of aging - i.e. partial rejuvenation was achieved. Another micronutrient, curcumin, induced an 11% lifespan extension when started in mid-life (approximately equivalent to 35 human years), but only produced 3% lifespan extension when started later (approximately equivalent to 50 human years),[7] implying aging retardation but not rejuvenation.

Summary: don't wait until too late.

Unproven but Probable Anti-Aging Enzymic Cofactors

Since B vitamins B_5 (pantothenate) and B_6 (pyridoxine) have extended mammalian life span, and B_3 (niacinamide), B_9 (folate) & B_{12} (cobalamin) are a proven health boosters (and hence probable life span extenders) it is worth considering supplementing with all the B-vitamins. Collecting together the range of B-vitamins and minerals which haven't been tested for their life extending effect, on mammals, but which have demonstrated considerable health benefits in humans, we have:

- Thiamine (vitamin B_1)
- Riboflavin (vitamin B_2)
- Niacinamide (vitamin B_3)
- Biotin (vitamin B_7)
- Folate (vitamin B_9)
- Adenosyl- & methyl-cobalamin (vitamin B_{12})
- Magnesium
- Carnitine
- Alpha-lipoic acid
- Zinc

Vitamin B_9 (folate), as we have seen, is critical for adequate methylation. If it passes the lifespan test then we would consider it an anti-aging micronutrient. Vitamin B_{12} (cobalamin), likewise, is critical for methylation, along with

some additional functions. It too may have anti-aging properties. If magnesium exerts an anti-cancer effect via genomic stability, in addition to its cardio-vascular protective effect, then it to may be considered an anti-aging candidate. Zinc may have an indirect anti-glycation effect[91], which would make it an anti-aging candidate.

Coenzyme Q10, carnitine and lipoamide (another coenzyme) are all synthesised internally, like SAMe, although in sub-optimum amounts. Co-Q10, lipoamide and carnitine look like promising life extenders[32] in combination, if not singly. Carnitine and lipoamide separately, and even more so together, have rejuvenated old rodents, measured across multiple parameters[37a-c], as we've already seen, although CoQ10, given alone, increased ROS production[4]. Again it may be worthwhile taking the B-vitamins, C and minerals to boost CoQ10, carnitine and lipoamide's biosynthesis before considering direct supplementation. For CoQ10 this makes especial sense, since our gut poorly absorbs it.

A defining and irritating drawback with this 2nd category of dietary enzymic cofactors is that we have no hard numerical data for calculating an expected lifespan extension effect. Statistically we might expect – in the Bayesian sense - the life extension effect of the probable anti-aging 6 enzymic cofactor-precursors (vitamins B_1, B_2, B_3, B_7, B_9, B_{12}, magnesium, zinc, carnitine and alpha-lipoic acid; 18 cofactors) to be more than 85% yielded by the 4 known anti-aging enzymic cofactor-precursors (vitamins B_5, B_6, RNA and chromium; 9 cofactors). Note, this argument is independent of whether we enumerate the cofactors or their precursors, since RNA is a precursor to 5 coenzymes, B_2 and B_3 are precursors to 2 coenzymes each, whilst the folates are a class of 6 coenzymes.

If all the probable anti-aging enzymic cofactors work then an additional mean life extension of 85% *18/9 = 170% is expected. In practice we must expect that some will be duds, so we must qualify our expectation and say that a total mean lifespan extension is to be expected somewhere in the range of 85% to 255%. A doubling or tripling of our natural lifespan would be a reasonable expectation.

Micronutrients that improve health, but may not delay aging:

Non-(enzymic cofactor) micronutrients may square the survival curve, but they are unlikely to extend it as a true anti-aging micronutrient would. Most of the anti-oxidants (see above) I include in this category.

Vitamin C: hard to extrapolate anything from experiments on rodents, since nearly all non-primates mammals (e.g. rodents) synthesise ascorbic acid naturally. Primates, including humans and fruit bats, have lost the ability to synthesise ascorbic acid due to the high amounts in their fruit-rich diet. The average human ingests more than 2.5 g/day before increased excretion occurs, which suggests that our metabolic requirement for this vitamin is in the multi-gram /day range[77]. Vitamin C alone[14], and in conjunction with vitamin E[13], has reduced overall mortality rates in humans and would presumably raise average life span at least.

Human growth hormone, melatonin & DHEA – are all synthesised naturally, with their synthesis dependent on dietary enzymic cofactors. Rather than take these hormones directly – oral intake of each may have downsides[22, 39a, 39b, 68a] or simply be ineffective[68b] - I prefer to boost the body's own synthesis by supplementing with a range of their precursor cofactors, such as the B-vitamins and minerals. Chromium picolinate, for instance, has been shown to boost DHEA levels in the middle-aged and elderly[20, 21]. And boosting the body's production of SAMe (the coenzyme responsible for all methylation reactions), with B_6 (pyridoxine), B_9 (folate) and B_{12} (cobalamin)[118] also aids in the conversion of serotonin (a neurotransmitter) to melatonin.

Selenium, as we have already seen, is effective in reducing cancer rates[15, 16, 72], but may have too narrow a range of action to delay aging.

The carotenoids (e.g. alpha- & beta-carotene, lycopene) are naturally occurring pigments in plants which step down the harmful high frequency ultra-violet (UV) light to lower frequency, less harmful and more visible, wavelengths. Plants produce them to simultaneously utilise and protect against UV. By ingesting them we can also acquire partial protection from UV damage. Carotenoids are also anti-oxidants. Beta-carotene, for instance, is a quencher of singlet oxygen and free radicals, which may account for beta-carotene and lycopene preventing prostate[70] and liver[67] cancer.

Their health benefits extend beyond their antioxidant properties, though. For instance lycopene actually inhibits the tumour growth and proliferation of prostate cancer[66].

There is no reason to think of herbs, such as garlic, the bio-flavonoids[108], silymarin, ginseng, as anti-aging, with one exception, ginger[7], yet they have many medicinal uses, including preventing cancer and cardio-vascular diseases[96].

Myths and Fallacies

We are entitled to wonder why the medical establish is so slow to advocate the widespread use of micronutrients as a prophylactic measure. The usual reasons cited include lack of corporate interest in promoting unpatentable, ergo unprofitable, vitamins and minerals, lack of nutritional training for medics plus the medical skew towards treatment rather than prevention.

In addition there are some scientific fallacies or myths that delay the wider acceptance of supplemental micronutrients. Vitamins, herbs and minerals are natural which, as far as most medics are concerned[96c], makes them inferior to drugs. At the same time, because they are natural, most evolutionary biologists believe that the amounts in our diet must already be close to or at the optimum, in which case supplements are wasted. Some of the measures used by gerontologists to measure the effectiveness of anti-aging regimes are biased against micronutrients. Let's look in more detail at these ideas:

Natural Diet is not Optimal

The switch from a hunter-gather diet (nuts, berries, wild game, roots) to one based on agriculture, about 7000 years ago in the Middle East, was accompanied by a drop in average height of up to 6 inches (only regained in the West during the 20th Century); a compelling sign that the reduced food diversity that accompanies agriculture abundance resulted in widespread chronic malnourishment[28a]. What about modern diets, are they optimally healthy? Supplying more than the RDA of many micronutrients to already healthy people further improves their health, as demonstrated by many placebo-controlled trials[47-61] and epidemiological studies[11-14], a view finally endorsed in a JAMA review[82]. This demonstrates that our modern diet, although superior to any since hunter-gatherer days, still borders on malnourishment.

What about the pre-agricultural-farming Palaeolithic hunter-gatherer diet, perhaps **that** diet (nuts, berries, wild game, roots) is optimal? That we have deviated from this 'natural' diet is beyond dispute. If only, the myth says, we would eat like cavemen, we would be much healthier. The belief that the 'natural' diet is optimal seems to arise from a misunderstanding of evolution. The argument runs thus: we have evolved to optimise the metabolising of dietary micronutrients; therefore the amounts of various micronutrients in our natural diet must be optimal. This is a simply faulty logic – the conclusion (amounts of various micronutrients in our diet must be optimal) doesn't follow from the premise (we have evolved to optimise the metabolising of dietary micronutrients).

The same illogic applies to macronutrients, where it is easier to demonstrate this fallacy. Water is a macronutrient, which our thirst mechanism fails to regulate optimally, leaving us marginally, chronically dehydrated[76]. For our savannah ancestors paying a visit to the watering hole was an expensive, time-consuming and risky activity due to increased exposure to waterhole predation, water-borne parasites and diseases; under these circumstances partial dehydration is a worthwhile trade-off. Our thirst mechanism is not adjusted, in the evolutionary sense, to the availability of clean, cheap water in the modern world; drinking more water than we naturally feel inclined to may be beneficial to our health[75].

The same is true for feeding. Feeding, for most of our evolutionary history, has been an expensive, risky activity, involving a number of trade-offs, forcing a compromise with marginal malnutrition. Herbivores face increased predation whilst grazing and carnivores risk injury whilst hunting, for example. This makes feeding a risky activity. Feeding halts when the marginal benefit of the extra calories is outweighed by the associated foraging risks; marginal malnourishment, due to inadequate amounts of some or all micronutrients in the diet, will not necessarily generate a feeling of hunger.

Incorrect Dosage Scaling

Drug dosage in the literature is often expressed in units per kilogram, which yields an inappropriate inter-species scaling up by body weight; smaller mammals (e.g. rodents) generally have a higher metabolic rate per unit weight, processing food and drugs at a faster rate than larger mammals (such as humans). scaling up dosage by body weight from a smaller to larger animal can lead to toxic dosages. For instance, scaling the rodent B_6 (pyridoxine) dose up by body weight we get a human dosage of approximately 10grams/day, which would be well into the toxic range[32], as low as 2g/day[40]. The number of calories consumed, not body weight, scales the dosage extrapolation (Appendix B) from rodent to human. Scaling up the B_6 (pyridoxine) dosage by calories, rather than body weight, yields the safer 720mg/d extrapolation.

Scaling by weight has lead to two errors. First, extrapolating dosage from rodents to humans by body weight overestimates the human requirement, leading, sometimes, to toxic recommendations[32, 40], undermining confidence in the validity of animal models. Second, extrapolating from known human requirements back onto rodents has lead to underestimating the requirements for rodents and yielded an influential negative lifespan study[42]. The amounts of various the B-vitamins, used in this negative study[42], when adjusted for calorific intake, were barely at the modern RDA level. The correct procedure for extrapolating nutrient requirements is to scale body weight ratios to the power of ¾, as we have already seen.[81a-c]

The incorrect scaling has also led to an overestimate of requirements for vitamin B_5 (pantothenate) amongst the health industry, with recommendations into the multi-gram/day range when, as we have seen, just over a 120 mg/d is probably sufficient. For vitamin B_5 (pantothenate) this overdosing is not important since it completely non-toxic. But for vitamin B6 (pyridoxine), as we have seen, the overestimate induced by incorrect scaling is more serious, since the anti-aging dose (720 mg/d) is close to the toxic dose (2 g/d) [40].

Recommended Daily Allowances (RDAs)

The recommended daily allowance, or RDA, of a particular micronutrient is often set at the amount of a micronutrient required to either prevent the appearance of the appropriate deficiency syndrome (e.g. rickets, scurvy, beri-beri) or maximise the activity of a selected enzyme. The amounts required to achieve significant life-extension are often between 30 to 400 times these RDA levels.

Complexity of Aging

Aging, as we have seen, is a multifactorial process. Drugs are designed to be target-specific, although they usually have multiple unwelcome side effects. A single drug treats a single disease. So it is unreasonable to expect that a single "magic bullet" drug is going to stop or reverse a complex process such as aging. Micronutrients, such as the precursors to enzymic cofactors, on the other hand, affect the metabolism at a very primitive level via the action of innumerable enzymes at the sub-cellular level; the effect of dietary enzymic cofactor precursors is not specific to a single tissue or organ, but is usually system-wide. It is entirely possible for something as broad as aging to be affected by micronutrients, via their effect on the enzymic cofactors, in a way that target-specific synthetic drugs simply can't do.

Vitamin Scare Stories

Even amongst professional medics[33a] myths about the toxic effects of vitamins circulate and hamper their wider acceptance. The story about vitamin C and B_6 (pyridoxine) causing kidney stones, for instance, is still regularly trotted out by medics and given considerable media exposure, despite it never having any empirical basis[33a] and actually disproved in 1996.[89]

Species Maximum Lifespan

Many researchers, for example Walford[33], use species maximum lifespan as the only test of whether an intervention is truly anti-aging or not. If cohort maximum lifespan exceeds the current species maximum lifespan they accept it

as an anti-aging intervention, otherwise not. There are three fundamental problems with using species maximum lifespan as such a gerontological yardstick.

First, the raising of the species maximum lifespan by discovery of a longer-lived strain[34] within the species or creation of a longer-lived strain by selective breeding[35] invalidates the species maximum as a meaningful yardstick with any stability.

Second, use of the species maximum lifespan assumes that aging is a constant across a species. This seems rather arbitrary. Why not the select the phylum, order, class, genus, strain or even - as seems most likely - the individual[65] as the level of zoological classification at which the rate of aging is presumed constant?

Third, species maximum lifespan is a statistically unfair comparison. A species maximum lifespan is typically defined against a reference population of millions of animals, whereas the number in the experimental cohort only defines the cohort lifespan. In any very large population, such as the entire species, the laws of probability decree that some very long-lived individuals will always occur (such as Jeanne Louise Calment, who lived to 122), whereas in a smaller population this is very unlikely (any of **your** relatives live to 122?). For this reason, whilst an experimental cohort which exceeds the species maximum is statistically very significant (e.g. for chromium picolinate), failure of a cohort to exceed the species maximum is statistically meaningless.

Inadvertent or Crypto- Calorie Restriction

Calorie Restriction

Calorie restriction has extended the life span of a number of species, including mammals[33]. An animal on a calorie-restricted diet receives the full compliment of essential micronutrients (vitamins and minerals) but the calorific intake is restricted. Calorie-restricted animals only show extended lifespan when their restricted diets are enriched with increased concentrations of vitamins and minerals. Indeed it is this extra dietary micronutrient enrichment that distinguishes dietary restriction, which doesn't extend lifespan, from calorie restriction, which does extend lifespan[28a].

The life-extending mechanism of calorie restriction is probably related to glycation, although other effects may also be operative, such as the switch from anaerobic to aerobic metabolism[120]. Calorie restricted animals have lower fasting glucose and insulin levels and improved glucose tolerance. It may be relevant that diet restriction has been shown to increase the concentration of some vitamer coenzymes in body tissues[29]. This implies that the calorie restriction will also raise coenzyme levels, since calorie restriction is enriched diet restriction. If so this nicely dovetails with the hypothesis of Guarente, Sinclair et al about the interaction of the SIR2 gene and NAD (a coenzyme) to produce the calorie-restriction life-extension effect[27a, 27b].

Crypto- Calorie Restriction

Sometimes the apparent anti-aging effect of a supplement is an artifice of inadvertently induced calorie restriction on the experimental animals. According to the hypothesis of crypto-calorie restriction the experimental animals are put off their food by the supplement's unpleasant taste, eat less food & fewer calories and so experience the age-retarding effect of calorie restriction. To eliminate this effect the weight or dietary intake of the experimental animals must be compared and controlled for. If not a hidden or crypto- calorie restriction may induce the lifespan extension that will be falsely attributed to the dietary micronutrient.

This criticism does apply to the anti-aging micronutrients discussed here, namely dietary RNA, vitamin B_5 (pantothenate) & B_6 (pyridoxine) and the mineral chromium (as chromium picolinate). The weight of the experimental animals given extra dietary RNA [2a] and vitamin B_5 (pantothenate) [3] actually exceeded, slightly, the weight of the controls, so a crypto-calorie restriction effect could not be operative here. No reduction in food intake was observed in the experimental animals given vitamin B_6 (pyridoxine)[6], so again crypto-calorie restriction can be excluded as the mechanism for the observed lifespan extension.

Only with chromium would crypto-calorie restriction appear, at first sight, a theoretical possibility. Diet and weight were not reported in the chromium experiment, and a drop in insulin and glucose levels and the glycation rate were observed[5a], all of which are associated with calorie restriction. But the drop in insulin and glucose levels and glycation rates have also been observed in many non-lifespan experiments with chromium, where diet restriction was not a possibility, so there is no need to invoke calorie-restriction to explain the lifespan effect, since glycation is already widely implicated in aging[83]; the anti-glycation effect of chromium is a sufficient explanation on its own to explain the associated lifespan increase.

Conclusion

In order of decreasing probability, we can expect dietary supplements to yield a mean average lifespan increase of at least either:

- 27%. Extrapolating purely from the mammalian lifespan data. Assumes no synergy between the known anti-aging micronutrients (enzymic cofactors) dietary RNA[2], chromium[5] and vitamins B_5 (pantothenate) [3] and B_6 (pyridoxine) [6], which is unrealistically pessimistic.
- 85%. Extrapolating from both the insect and mammalian lifespan data. Allows for synergy[1b] between the known mammalian anti-aging enzymic cofactors and vitamin B_3 (niacinamide) [4].
- 85% to 255%. Extrapolating from additional probable anti-aging micronutrients, the enzymic cofactors magnesium, zinc, carnitine, alpha lipoic acid and vitamins B_7 (biotin), B_9 (folate) and B_{12} (cobalamin)). If all the probable anti-aging enzymic cofactors work then an additional mean life extension 170% is expected. A more realistic total mean lifespan extension would be somewhere in the range 85% to 255%; a doubling or tripling of our mean average natural lifespan, 70 years, to between 140 and 250 years would be a reasonable expectation.

We can expect an associated maximum lifespan increase of approximately 63%[5, 7] of the mean average lifespan increase, i.e. in the range 54% to 145%, to total 188 to 300 years.

Use of the health boosting micronutrients: selenium[15, 16, 72], the carotenoids[67, 70], flavonoids[108] various herbs[96] and the remaining "unofficial" B-vitamins B_4 (choline), B_8 (inositol) & B_{10} (para-aminobenzoic acid) may help square the survival curve, raising the mean life span closer the new maximum lifespan. Living to, and beyond, 200 years is achievable right now.

Cautions and Caveats

Some micronutrients can be toxic, or have unwanted side effects, in large amounts. There is a great deal of biochemical variation between people; what is an appropriate for one individual may make someone else sick. You should consult a mainstream doctor before starting to megadose and have your medical condition monitored carefully.

Some other factors to consider:

Beware of the "rebound effect"; sudden cessation of the intake of a vitamin may induce a temporary depletion in that vitamin to below pre-supplementation levels and occasionally the appearance of the associated deficiency syndrome. This can be avoided by gradually reducing your intake over a period of weeks, rather than suddenly. The rebound effect has been observed with vitamin C (ascorbic acid) when intake was dropped from 10g/d to 125mg/d[44]. The rebound phenomenon is actually evidence for the effectiveness of high doses of vitamins and disproves the common mythology that excess vitamins are wasted. As the study[44] found "We hypothesize that the high intake of ascorbic acid has induced the formation of increased amounts of enzymes that help convert the ascorbic acid into other substances and that these substances are valuable."

A large dose of a single B-vitamin tends to deplete levels of the other B-vitamins[43a-c]. To avoid this ensure you're getting enough B_5 (pantothenate) & B_6 (pyridoxine) via B-complex supplements (which should supply adequate amounts of most of the other B-vitamins) and then take additional B_3 as niacin, which is required in much larger amounts than the other B-vitamins.

Vitamin B_3 (as nicotinamide) may be toxic in the range 3-6gm/d[85]. Niacin is generally considered less toxic[40], but, still, in some individuals large doses of niacin have caused abnormal liver behaviour. Also niacin can cause an uncomfortable, although, as far as we know, harmless and temporary skin flushing. Taking as inositol hexanicotinate, which is generally regarded as non-toxic, unlike some other slow-release formulations[73], removes this problem.

Neurological problems been observed with vitamin B_6 (pyridoxine) in doses of over 2 g/d[40]. The toxicity observed with B_6 may or may not be due to depletion of other un-supplemented B-vitamins. Extra B_2 (riboflavin) and magnesium may aid the conversion of pyridoxine to the safer, active form, pyridoxal-5-phosphate[73]. More than 200mg/d of B_6 (pyridoxine) has been reported to induce a dependency[32]. As with the rebound effect this is actually an indication that the high dose is metabolically active, rather than wasted, as many authorities believe. Nevertheless, going cold turkey is probably an experience to be avoided. As with the rebound effect, should you decide to stop supplementing, the advice is to taper off any high intakes slowly, rather than quickly.

B_9 (folic acid) should always be taken with vitamin B_{12} (cobalamin), since folic acid may mask some of the signs of a B_{12} deficiency (e.g. anaemia) without correcting some of the other associated neurological deficits.

Oral consumption of both melatonin[22] and DHEA[68a] has been linked, in some animal models, with increased tumour occurrence. Human growth hormone may actually accelerate aging[39a, 39b]. Personally, I don't advise taking any hormone supplements. They may make you feel great, but could be doing a lot of harm.

Selenium is toxic in the milligram range, with claims for the toxic starting level between 900ug/d[73] to 6000ug/d[72a]. The organically-bound forms (e.g. selenomethionine) are safer than the inorganically bound forms of selenium (e.g. sodium selenate).[72a] Concurrent magnesium supplementation is advisable since magnesium may provide some protection against selenium toxicity[45].

RNA rich diets may elevate uric acid levels. For people susceptible to gout this could a problem. Check with an expert beforehand, especially if there is a family history of gout.

The list of minerals covered here is not complete. There are many more metallic ion cofactors (boron, vanadium, molybdenum, copper, manganese etc, etc), which the constraints of time and space preclude from detailed inclusion here[73].

Do not megadose with the fat-soluble vitamins, especially vitamins A, D and E. Although not discussed much here, for they are not coenzyme precursors, be aware that A & D toxicity is high and a dangerous dose is easy to accumulate, since, not being water-soluble, they are not readily excreted. If taking a number of multivitamins, try to avoid those with vitamin A. Vitamin A is probably the easiest to overdose on. To avoid vitamin A toxicity take alpha-, beta- or gamma-carotene or cryptoxanthin instead, which your body will convert into vitamin A, as needed. Some of the other carotenoids, e.g. lycopene & lutein, although they have their own benefits, don't convert to vitamin A. Large amounts of the carotenoids will colour the skin, although this is not harmful.

Although beta-carotene decreases the risk of lung cancer for non-smokers or ex-smokers, it may increase the risk for current smokers[71], at least in the short term, unless they also supplement with vitamin E[69]. Other carotenoids have not been as thoroughly tested and may also have the same effect.

Iron – often advised for anaemia - is not generally needed and can be harmful[99]; a vitamin B_9 (folate) or B_{12} (cobalamin) deficiency more often causes anaemia.

The author does not possess any biological or medical qualifications! Do your own reading of the subject. A good starting point is the Encyclopedia of Nutritional Supplements. Michael T Murray, (1996) ISBN 0761504109. An invaluable resource; should be read by everybody prior to supplementing. Of course this advice would be pertinent even were I a Nobel laureate.

Coenzyme(s)	Source	Action facilitated	Comments
Adenosine Triphosphate (ATP)	Synthesised de novo and from dietary RNA	Transfer of phosphoryl or nucleotidyl groups	Supplies the energy for a lot of reactions
S-Adenosylmethione (SAMe)	Synthesised from methionine	Transfer of methyl (CH3) groups	Levels may be raised by supplementing with vitamins B_6 B_9 & B_{12}
Ubiquinone / Coenzyme Q10 (Co-Q10).	Synthesised	Lipid soluble election transfer	Levels may be raised by supplementing with vitamin C, the B-vitamins and minerals
Thiamine pyrophosphate (TPP)	From dietary thiamine (vitamin B_1)	Transfer of 2-carbon units containing a carbonyl group	Deficiency causes beri-beri. Counters insulin-resistance
Flavin mononucleotide (FMN) & flavin adenine dinucleotide (FAD)	From dietary riboflavin (vitamin B_2)	Oxidation-reduction reactions involving both 1- and 2-electron transfers	Often relays electrons to and from NAD+/NADH & NADP+/NADPH
Nicotinamide adenine dinucleotide (NAD+/NADH) & nicotinamide adenine dinucleotide phosphate (NADP+/NADPH)	From dietary niacin (vitamin B_3), although can also be synthesised less efficiently from dietary tryptophan	Oxidation-reduction reactions involving just 2-electron transfers. Also a substrate to PARP	Dietary deficiency causes pellagra NAD is important in modulating ADP-ribose polymer metabolism, cyclic ADP-ribose synthesis, and stress response proteins, such as p53, following DNA damage. Critical for DNA repair. Helps prevent diabetes
Coenzyme A (CoA)	From dietary pantothenate (vitamin B_5)	Transfer of acyl groups	Provides increased resistance to physiological stress
Pyridoxal-5-phosphate (PLP)	From dietary pyridoxine (vitamin B_6)	Transfer of groups to and from most amino acids	Required for all protein synthesis
Biotin	Absorbed from intestinal bacteria and dietary biotin (vitamin B_7)	Carboxyl-group transfers and ATP-dependent carboxylation	High doses help regulate insulin secretion and alleviate diabetes
Tetrahydofolates: 6 inter-convertible foyl coenzymes	From dietary folate (vitamin B_9)	Transfer of a range of 1-carbon groups	Required for biosynthesis of nucleotides, particularly thymine for DNA.
Tetrahydrobiopterin	Synthesised with the aid of 5-methyltetrahydrofolate and vitamin B12	Cofactor for several hydroxylases, e.g. phenylalanine hydroxylase	Required for the biosynthesis of tyrosine from phenylalanine, biosynthesis of catecholamines and indolamines, and the neurotransmitters serotonin and dopamine.
Adenosylcobalamin	From dietary cobalamin (vitamin B_{12})	Interchange of a hydrogen atom and an adjacent side chain on a carbon backbone	
Methylcobalamin	From dietary cobalamin (vitamin B_{12})	Transfer of methyl groups	Required for regeneration of methionine from homocysteine
Vitamin K	Vitamin K	Carboxylation of some glutamate residues	Fat-soluble
Uridine diphosphate (UDP) glucose	Uracil from dietary RNA	Glucose donor. Transfer of glucosyl groups	Required for biosynthesis of glycogen
Uridine diphosphate (UDP) glucuoronic acid	Uracil from dietary RNA	Transfer of glycosyl groups	Required for biosynthesis of glycosaminoglycans and tetrahydro-curcumin-glucuronoside[74] from curcumin
Cytidine diphosphate-choline/ ethanolamine/ diacylglycerol	Cytosine from dietary RNA	Lipid biosynthesis	
Carnitine	From diet and synthesised	Co-substrate for carnitine acyltransferase I & II, required for the transport of fatty acyl groups into the mitochondria	Critical for mitochondrial energy release
Lipoamide (lipoate)	From lipoic acid in diet and synthesised	Oxidation of a hydroxyalkyl group from TPP and transfer as an acyl group	

Appendix B Dosage Extrapolation

The dosage extrapolations are from the amounts that have had either extended lifespan or, in the absence of definitive lifespan data, had the maximum physiological effects on animals (where possible, humans). To allow for metabolic differences between larger and smaller mammals I scaled micronutrient dosage by calories; the equivalent to maintaining the same micronutrient density, i.e. amount per weight of feed. For calculational purposes I assumed a human intake of 2500 calories/day, with a dry feed weight of 1kg/day. Where direct information on calorific intake was not available I have scaled by total metabolic turnover, using the established ¾ power scaling law[81a-c], which should be approximately equivalent to calorific scaling.

Dietary Enzymic Cofactor(s)	Extrapolated Optimal Daily Dose	RDA for adult male/female	Toxic Daily Dose
Thiamine (vitamin B_1)	3 – 8 gm [106]	1.5/1.1 mg	
Riboflavin (vitamin B_2)	10 mg [102]	1.7/1.3 mg	
Niacinamide (vitamin B_3)	5 g [27f, 27c]	19/15 mg	3-6gm[85]
Pantothenate (vitamin B_5)	120 mg [3]	4/7 mg	
Pyridoxine (vitamin B_6)	720 mg [6]	2.0/1.6 mg	2 g[40]
Biotin (vitamin B_7)	3[93] - 9 mg [55d]	300 ug	
Folate (vitamin B_9)	926 ug [49]	200/180 ug	
Adenosylcobalamin (vitamin B_{12})	50 [50b] – 500 ug[50a]	2 ug	
Methylcobalamin (vitamin B_{12})	2 [101a] - 10 mg [101b]	2 ug	
Magnesium	1-2 g	350/280 mg	
RNA	250 mg [2a]	-	
Chromium picolinate	1 mg (Cr) [5a-e]	-	
Carnitine	1.5 – 4 gm [73]		
Alpha-lipoic acid	600 mg [98] - 5 g	-	
Zinc	25 [90]-30 mg[91]	15 mg	150 mg[73]
Other Micronutrients			
Selenium	400 ug [16]	-	900ug[73] - 6000ug[72a]
Beta-carotene		-	60mg (smokers only)
Lycopene	30 mg [66]		
Curcumin	2 gm [7]	-	
Vitamin C	2.5 gm [77]	60 mg	
Vitamin E (alpha-tocopherol)	400 IU [73]	10 mg / 15 IU	

g = gram, mg = milligram, ug = microgram

Glossary

Apoenzyme – The inactive form of an **enzyme**, formed from amino acids and/or nucleotides. Requires the presence of specific enzymic **cofactors** to function.

B-vitamins – a range of water-soluble vitamins, some of which are converted in our bodies into **coenzymes**. The B-vitamins are thiamine (B_1), riboflavin (B_2), niacin (B_3), choline (B4), pantothenate (B_5), pyridoxine (B_6), biotin (B_7), inositol (B_8), folate (B_9), para-aminobenzoic acid (B_{10}) and cobalamin (B_{12}). Some classifications do not include B_4, B_8 and B_{10} , non of which are **coenzymes**, as B-vitamins and some have the labels B_3 and B_5 interchanged. Only the B-numbers B_1, B_2, B_6 & B_{12} have universally agreed usage.

Coenzyme – a coenzyme is a complex molecule that an **enzyme** requires in order to function. The coenzymes either bonds permanently onto the enzyme, forming a prosthetic group, or is required as a co-substrate by the **enzyme**. **Apoenzymes**, with the exceptions of **ribozymes**, are proteins constructed from amino-acids. This limits the range of their flexibility or activity. The coenzymes, by contrast, are not amino-acid based, and supply the more diverse arrangements of molecules that **apoenzymes** require to complete their structure and function correctly as **holoenzymes**. In general a particular coenzyme performs one just biochemical action, but **enzymes** and coenzymes have a many-to-many relationship; a particular **coenzyme** is typically is required by a number, sometimes hundreds, of different **enzymes** and, conversely, one **enzyme** may require the presence of many coenzymes to function.

Some **coenzymes** are synthesised by our body, others are derived from the **B-vitamins** in our food. See Appendix A for a full list of coenzymes.

Cofactor – an enzymic cofactor is either a metallic ion or a **coenzyme**, which an inactive **apoenzyme** requires to function or become activated as a **holoenzyme**. Many different **enzymes** require the same cofactor(s) to function.

Enzyme – an enzyme is a protein molecule (a chain of amino acids, with the exceptions of **ribozymes**) produced in our body, that controls the rate of a reaction. Enzymes control virtually all reactions. Each enzyme is specific to one particular reaction or step in a metabolic pathway. There are thousands of different reactions on our body, each with their own enzyme. The same enzyme may be active in different tissues and organs.

DNA – deoxyribonucleic acid, a double-stranded repository of genetic information. Contained in the cell's nucleus and mitochondria.

Glycation – (non-enzymic **glycosylation**) the harmful, uncontrolled bonding of free glucose to other molecules, particularly the amine tails of proteins, creating cross-links and, in **DNA**, mutations. The rate of glycation is proportional to the level of free glucose. Thought to be one of the major causes of aging.

Glycosylation – the enzymic-mediated transfer of glucose reactions. These reactions are vital and not harmful. Cf **Glycation**

Hayflick Limit – after Leonard Hayflick, who discovered that most tissue cells, when allowed to proliferate freely in the laboratory, cease dividing after a pre-set number of divisions; a milestone on gerontology, at the time, and widely seen, nowadays, as evidence for telomeric control.

Holoenzyme – The activated functional form of an **enzyme**.

Niacinamide – also known as nicotinamide. Its carboxylic acid analogue is nicotinic acid or niacin, vitamin B_3.

PARP - poly(ADP-ribose) polymerase. An enzyme involved in the generalised excision-repair pathway, critical for repairing **DNA** damage.

RDA – the Recommended Daily Allowance is the amount required to eliminate a clinical deficiency. Values set by the Food and Nutrition Board of the National Research Council, 1998.

RNA – ribonucleic acid, a form of nucleic acid. Two types. Messenger RNA (mRNA) conveys the information in **DNA** from the nucleus to ribosomes, where transfer RNA (tRNA) helps assemble the proteins from the instructions from the mRNA.

Ribozyme – A small number of important non-proteonomic enzymes are formed from nucleotides, not amino acids. These **enzymes** are believed to be the most ancient, evolving before the more numerous proteonomic **enzymes**, and still play a pivotal role in metabolism.

Telomeres – repeating sequences of DNA at the end of chromosomes. As cells divide their telomeres shorten, which is why children have longer telomeres, on average, than adults. Eventually, after sufficient cell divisions, as

telomeres become too short the cells reach the Hayflick limit, cease dividing (replicative senescence) or even die (apoptosis).

Vitamin – a complex dietary micronutrient molecule, which we need to live, and which must be derived from our food, since we can't synthesise it. Some vitamins are water-soluble and some are fat-soluble, depending on which part of the body they are active in. Not all vitamins are precursors to **coenzymes**.

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Editorial note:

The article is under constant revision - for the latest version, please see http://www.longevity-report.com/lr91.htm or email the author at michaelprice@ntlworld.com.

The author is also interested in entering into email discussion about the points raised.