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Increasing longevity by tuning up metabolism

To maximize human health and lifespan, scientists must abandon outdated models of micronutrients

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Our daily intake of the 40 essential micronutrients—vitamins, minerals and other biochemicals—is commonly thought to be adequate. Indeed, classic deficiency diseases, such as scurvy, beriberi and pernicious anaemia, are now rare among the citizens of developed countries. The optimum amount of vitamins, minerals and essential biochemicals is the amount that maximizes a healthy lifespan, and is likely to be higher than the amount needed to prevent acute deficiency disease. Evidence suggests, however, that much chronic metabolic damage occurs at levels above the level that causes acute micronutrient deficiency disease but below the recommended dietary allowances (RDAs). In addition, current RDAs may not be sufficient to prevent subtle metabolic damage: if one input in the metabolic network is inadequate, repercussions are felt in a large number of other systems. This could result in an increase in DNA damage (and cancer), neuron decay (and cognitive dysfunction) or mitochondrial decay (and accelerated ageing and degenerative diseases). In addition, the optimum amount of micronutrients varies with age and constitution—the requirements of the elderly for vitamins and metabolites are likely to be different from those of the young—and with genetic make-up. A tune-up of micronutrient metabolism should therefore markedly increase health at little cost. It is a distortion of priorities for much of the world's population to have an inadequate intake of vitamins or minerals—at great cost to health—when a year's supply of a daily multivitamin/mineral pill costs less than a few packs of cigarettes. The poor, in general, have the worst diets and have the most to gain from improving their multivitamin and mineral supplementation and diet.

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For most of human evolution, caloric shortage probably limited population growth. As food was mostly calorie-poor and unprocessed, the supply of micronutrients may have been fairly adequate. The advent of agriculture changed that and made diets less varied. The introduction of the potato to Europe from South America in the late sixteenth century caused a major increase in the European population over the next few centuries as the cultivation of potatoes spread and as cultivars were selected that thrived in each climate. "In 1845 close to 40% of the population of Ireland lived chiefly on potatoes. The emergence of the 'potato people' occurred against the background of the quadrupling of the population after 1700…" (Clarkston & Crawford, 2001). Similarly, the cultivation of rice varieties was a major factor enabling high population density in Asia. Although caloric shortage is now a thing of the past for many people in Europe, Asia and North America, the abundance of carbohydrate- and fat-rich food causes another problem. Inexpensive, processed foods and drinks are calorie-rich but poor in micronutrients, and as a consequence, the USA and other developed nations are now facing an epidemic of obesity associated with micronutrient malnutrition (Kant, 2000).

Although optimal nutrition clearly requires more than micronutrients, such as fibre, there are important reasons to focus on micronutrients and health. More than 20 years of effort to improve the American diet has not been particularly successful with less-educated people, although this education initiative

must continue. A parallel approach that focuses on micronutrient malnutrition is overdue and might even be more successful—it should be easier to convince people to take a multivitamin/mineral pill than to change their diet. Such a pill is inexpensive, recognized as safe and supplies a range of required vitamins and minerals. Other micronutrients, such as essential omega-3 fatty acids, which are important for brain function and development (Simopoulos, 2001), and fibre, are also widely available and inexpensive.

Fortification of food is another useful approach, such as the addition of folate to flour, or calcium to juice. However, fortification of food does not allow for metabolic differences between individuals. Menstruating women, for instance, need more iron than men or older women, who in turn may be getting too much. That is why two types of vitamin pill are now marketed: one with iron for menstruating women and one without. With more knowledge of human micronutrient requirements, a variety of tailor-made multivitamin pills could therefore be developed to meet different needs depending on age, gender and genetics.

Giuseppe Arcimboldo (1573) *The Summer*, oil on canvas. Original: Musée du Louvre, Paris, France. Image provided by Gerard Le Gall, RMN, Paris, France. With permission from bpk, Berlin, Germany.

Micronutrient deficiencies can cause DNA damage, which may ultimately lead to cancer. Our strategy in the laboratory has been to use cultured human cell lines to show that deficiency of vitamins C, E, B12, B6, niacin, folic acid, iron or zinc appears to mimic radiation by causing single- and double-strand DNA breaks, oxidative lesions or both. This has serious implications as half of the US population may be deficient in at least one of these micronutrients (Ames, 2001; Ames & Wakimoto, 2002). Micronutrient deficiency may thus contribute to the increase of cancer incidence in the quarter of the population that eat the fewest fruits and vegetables, as compared with the quarter who have the highest intake. Although 5–9 portions of fruit and vegetables a day are advised, 80% of American children and adolescents and 68% of adults do not eat five portions daily (Ames, 2001).

Fruits and vegetables are a main source of folate, and low folate intake has been associated with several types of cancer (Ames & Wakimoto, 2002). Folate deficiency causes chromosome breaks due to the massive incorporation of uracil in the DNA (Blount *et al*, 1997). Before the recent folate supplementation of flour in the USA, 25% of the population and close to half of poor urban minorities had levels of folate intake that are associated with high uracil content and DNA breaks. As one would expect from mechanistic considerations, and as our research has shown, deficiencies (less than 50% of the RDA) of vitamins B12 or B6 also cause high levels of uracil incorporation in human DNA and chromosome breaks (Crott *et al*, 2001a,b). We are now attempting to determine the level of these three vitamins that minimizes both nuclear and mitochondrial DNA damage in humans.

Similarly, insufficient zinc causes oxidative DNA damage, inactivation of copper/zinc superoxide dismutase, inactivation of tumour suppressor protein p53—a zinc protein—and inactivation of oxidative DNA repair in cultured human cells, and these effects can multiply to cause severe genetic damage (Ho & Ames, 2002; Ho

et al, 2003). Zinc deficiency is associated with cancer in both humans and rodent models (Fong *et al*, 2005), but 10% of the US population ingest less than 50% of the RDA of zinc. Iron deficiency has also been shown to cause oxidative damage to mitochondria and mitochondrial DNA in rats (Walter *et al*, 2002; Atamna *et al*, 2002a). Among women of menstruating age in the USA, 25% ingest less than 50% of the RDA of iron. The poor are most affected as they have the lowest intake of these essential minerals (Frith-Terhune *et al*, 2000; Kumanyika & Krebs-Smith, 2001).

These common micronutrient deficiencies are likely to damage DNA by the same mechanism as radiation and many chemicals, but they seem to be more important by several orders of magnitude (Ames, 2001; Gold *et al*, 2002). Consequently, a sound public-health policy calls for micronutrient requirements to be set to minimize DNA damage (Fenech, 2003). The poor are clearly not well served if huge resources are put into preventing minor hypothetical risks, such as pesticide residues, while the major risk of poor nutrition is not addressed (Gold *et al*, 2002).

Vitamin-D deficiency is another major problem, particularly for people in northern areas. The hormone vitamin D is formed with the aid of ultraviolet (UV) light from sunlight, but too much exposure to UV light is dangerous. People who originate from northern areas with little UV radiation have light skin to maximize their exposure to UV rays, whereas people from southern areas have dark skin to minimize their UV light exposure. Dark-skinned people in northern parts of the USA are exposed to insufficient sunlight and individuals are often chronically vitamin-D deficient unless they drink fortified milk or take a supplement. "Although both dark- and light-skinned individuals can produce vitamin D in response to UV light, this response is much more limited in dark-skinned individuals. The 25-hydroxyvitamin D (25(OH)D) levels in African-Americans and Hispanics are, therefore, lower than Caucasians in the US" (Abrams, 2002). A study in the Boston area showed that 80% of African-Americans and 60% of Hispanics were vitamin-D deficient (Holick, 1994).

Vitamin D is necessary for calcium mobilization in bone formation, and a deficiency causes brittle bones. In addition, there is an inverse relationship between vitamin-D intake and the risk of several types of cancer, primarily colorectal cancer and colorectal adenomas; there is also evidence for a link to prostate cancer (Platz *et al*, 2000a,b; Levine *et al*, 2001; Holt *et al*, 2002). A plausible mechanism by which vitamin-D deficiency could increase cancer is the known inhibitory effect of vitamin-D metabolites on cell proliferation (Holt *et al*, 2002). African-Americans have almost double the prostate cancer rate of Caucasian Americans and also have lower levels of the vitamin-D metabolite 25-hydroxyvitamin D in their blood (Platz *et al*, 2000b). Recent epidemiological studies suggest that much of the increased cancer rate among African-Americans is in fact due to a vitamin-D deficiency.

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Dark-skinned people such as African-Americans and some Hispanics tend not to drink milk as adults, because of lactose intolerance. Europeans and other northern people domesticated cows thousands of years ago and over time developed the ability to metabolize lactose, a major sugar in cow's milk. Most of the rest of the world cannot use lactose as adults: 70% of African-Americans, 53% of Mexican-Americans and 90% of Asians are lactose intolerant compared with 15% of northern Europeans and their descendants. As African-Americans and Hispanics also tend not to take vitamin supplements, these individuals are all the more likely to be calcium, magnesium, potassium, folate and vitamin-D deficient (Kumanyika & Krebs-Smith, 2001). This illustrates why understanding genetics is important in some cases to develop appropriate interventions for populations at risk.

In addition to contributing to cancer and disease risk, micronutrient deficiencies have an effect on mitochondrial metabolism and thus accelerate cellular ageing. Haem biosynthesis takes place predominantly in the mitochondria and interfering with this process causes specific loss of haem-*a*, a component of complex IV, with a subsequent release of oxidants (Atamna *et al*, 2002a,b). Iron deficiency thus causes the release of oxidants and mitochondrial decay, presumably through the lack of haem-*a* (Walter *et al*, 2002; Atamna *et al*, 2002a). Biotin deficiency, which is quite common (Mock *et al*, 2002a,b), also causes defects in mitochondrial complex IV and induces oxidant leakage (H. Atamna *et al*, in preparation). There is also evidence that deficiencies in copper and pantothenate decrease levels of complex IV (Brambl & Plesofsky-Vig, 1986; Rossi *et al*, 1998). Zinc deficiency causes an increased release of oxidants, owing to the inactivation of δ-aminolevulinate dehydratase, an enzyme of haem biosynthesis that contains eight zinc atoms (Jaffe, 1995; Ho & Ames, 2002; Ho *et al*, 2003). The consequences of these various micronutrient deficiencies are likely to be accelerated ageing and neural decay (Atamna *et al*, 2002b; Atamna & Frey, 2004).

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The importance of vitamins and minerals for disease pathology is also highlighted by the fact that various diseases can be treated in part with high doses of micronutrients. As much as one-third of all gene mutations results in the corresponding enzyme having an increased Michaelis constant and thus a decreased binding affinity for its coenzyme, which results in a lower rate of reaction. Thus, many of the human genetic diseases that are due to defective enzymes can be remedied or ameliorated by the administration of high doses of the B-vitamin component of the corresponding coenzyme, which partially restores enzymatic activity (Ames *et al*, 2002). Some examples include C677T/Ala222Val methylenetetrahydrofolate reductase (NADPH) and the cofactor FAD in relation to cardiovascular disease, migraines and rages; the C609T/Pro187Ser mutation in NAD(P):quinone oxidoreductase 1 and FAD in relation to cancer; the C131G/Ala44Gly mutation in glucose-6-phosphate 1-dehydrogenase and NADP in relation to favism and haemolytic anaemia; and the Glu487Lys mutation,

common in Asians, in aldehyde dehydrogenase and NAD in relation to alcohol intolerance, Alzheimer's disease and cancer. The importance of binding affinity is also likely to be relevant for mitochondrial ageing as well as for human nutrition.

In fact, we are making progress in reversing some of the mitochondrial decay in aged rats by feeding them high levels of the normal metabolites acetyl carnitine (ALC) and R-lipoic acid (LA). The rationale behind this research is based on the observation that, with increasing age, oxidative damage to proteins causes a deformation in the structure of key enzymes, which reduces their affinity for the substrate (Liu *et al*, 2002a). The effect of age on decreasing the binding affinity of carnitine acyl transferase (CAT) for ALC or acetyl CoA can be mimicked by combining CAT with malondialdehyde, a lipid-peroxidation product that accumulates with age. Feeding rats ALC and LA restores the speed of the reaction for ALC transferase and mitochondrial function (Liu *et al*, 2002a). LA is an effective inducer of phase II antioxidant enzymes, including glutathione synthesis, as well as being a potent mitochondrial antioxidant (Suh *et al*, 2004a,b; Smith *et al*, 2004).

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In old rats, we can see that mitochondrial membrane potential, cardiolipin levels, respiratory control ratio and cellular oxygen uptake are lower when compared with young rats, whereas the ratio of oxidant by-product to oxygen consumed, neuron RNA oxidation and mutagenic aldehydes from lipid peroxidation are higher. Feeding these old rats ALC and LA for a few weeks restores mitochondrial function, lowers oxidant levels, neuron RNA oxidation and mutagenic aldehydes and increases rat ambulatory activity and cognition (Liu *et al*, 2002a,b; Hagen *et al*, 2002a). ALC and LA are also effective in protecting the ageing rat heart against cardiovascular decay (Hagen *et al*, 2002b). There is evidence that this might also benefit humans. A recent meta-analysis of 21 double-blind clinical trials of ALC in the treatment of mild cognitive impairment and mild Alzheimer's disease showed significant efficacy versus placebo (Montgomery *et al*, 2003). A meta-analysis of four clinical trials of LA for the treatment of neuropathic deficits in diabetes also showed significant efficacy compared with placebo (Ziegler, 2002).

Table 1 | Micronutrient deficiencies in individuals in the USA

Nutrient	Population group	RDA (μg)	Less than RDA consumption (%)	Less than half RDA consumption (%)
Minerals				
Iron	Women 20–30 years	18,000	75	25
	Women 50+ years	8,000	25	5
Zinc	Women/men 50+ years	8,000/11,000	50	10
Vitamins				
Folate*	Women 20+ years	400	75	50
	Men 20+ years	400	75	25
B6	Women/men 20+ years	1,500/1,700	50	10
B12	Women 20+ years	2.4	25	10
	Men 20+ years	2.4	10	5
C	Women/men 20+ years	75,000/90,000	50	25

*Folate intake before US fortification in 1998. RDA, recommended dietary allowance. Data adapted from Wakimoto & Block (2001); dietary intake includes food fortification but not supplement use.

In addition to the various deleterious effects on chromosomes and mitochondria described above, micronutrient deficiencies might have another serious effect on public health. The USA and other developed countries are facing an epidemic of obesity with related insulin resistance and type II diabetes. Although this epidemic is widespread in all groups, it is most prevalent among the poor and particularly in African-Americans and Hispanics. Sturm (2002) has estimated that the toll on health will be comparable with that of smoking. An energy-rich and micronutrient-poor diet could contribute in numerous ways to shortening life (Kant, 2000). Although the question has not been addressed experimentally, we hypothesize that micronutrient deficiency counteracts the normal feeling of satiety after sufficient calories are eaten. This may be a biological strategy for obtaining missing nutrients, which is important in fertility. Results from the Coronary Artery Disease Risk Development in Young Adults (CARDIA) study suggest that dairy-product consumption, the main source of calcium, is inversely related to obesity, diabetes and insulin resistance (Pereira *et al*, 2002).

Evidence is accumulating that a multivitamin/mineral supplement is good health insurance and would markedly protect us against heart disease, cancer, immune deficiencies and cataracts (Bendich *et al*, 1997; Oakley, 1998; Fairfield & Fletcher, 2002). The caveat, of course, is that too much of many minerals, such as iron, zinc, copper and selenium, and some vitamins, are toxic. Mae West's dictum about sex—"Too much of a good thing is wonderful"—does not apply to micronutrients. Advice on taking a multivitamin should always be coupled with advice on eating a good diet, as we also need fibre, omega-3 fatty acids and other ingredients (Willett, 2001). It is also good to keep Mark Twain's observation in mind: "The main distinguishing characteristic between man and the lower animals is the desire to take pills."

A metabolic tune-up through an improved supply of micronutrients is likely to have great health benefits, particularly for those with inadequate diets, such as many of the poor, young, obese and elderly. The issues discussed here highlight the need to educate the public about the crucial importance of nutrition and the potential health benefits of a simple and affordable daily multivitamin/mineral supplement. Tuning up metabolism to maximize human health and lifespan will require scientists, clinicians and educators to abandon outdated models and explore more meaningful ways to prevent chronic disease and achieve optimum health. It is becoming clear that unbalanced diets will soon become the largest contributor to ill health, with smoking following close behind.

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