

## The metabolic approach

### The must of our age

#### Summary

Metabolism is at the core of life. It creates the body and makes it work, reproduce, fight invaders, and age. When metabolic disruption goes beyond a certain limit the body falls ill or dies. The body is the macroscopic manifestation of a tremendously complex biochemical machine and as such metabolic features should always be considered at both the diagnostic and therapeutic stages. Disease and aging are based on metabolic changes which should be a primary target in the prevention and treatment of illnesses and physical and mental decline. The evidence in support of the role that type B malnutrition in developed countries plays in the development of aging and age-related diseases is rapidly increasing, as is that in favor of the role of targeted supplementation in improving a number of chronic and acute diseases as well as aging. Furthermore the tremendous increase in life expectancy that has occurred in the last century is unmasking a series of "snags" in human physiology which lead to the conclusion that the human body wasn't "designed" by natural selection to reach the average life expectancy currently achieved in developed countries. Targeted dietary supplementation has been shown to be of great importance in conditions such as cardiovascular disease, cognitive function decline, macular degeneration, male sub fertility, endothelial dysfunction, and many others. The metabolic approach is the targeted administration of micronutrients aimed at supporting or correcting the metabolic changes occurring in disease and aging and related to the suboptimal nutritional status of selected nutrients, in order to delay ageing thus improving the quality of life, particularly in the second half of it, and reducing the prevalence of chronic and degenerative diseases. This is also a powerful tool to reduce the social cost of chronic and degenerative diseases. Furthermore the metabolic approach is of paramount importance to positively modify the outcome of increased metabolic demand conditions such as acute diseases, stress, and intoxication. My conclusion is that targeted nutritional supplementation is currently a must in developed countries and as such healthcare professionals should look at it as an effective therapeutic tool in their armamentarium, to be employed alone or in combination with drugs and surgery to improve their outcome.

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## Metabolism and metabolic pathways

In spite of the complex network of reactions (too often felt as far from clinical reality) the word metabolism most of the time may bring to mind, this set of biochemical processes should be regarded by medical doctors in a more immediate manner.

Placing oneself in front of a mirror means watching metabolism itself: our body, its movements, its reactions to the environment “are” our metabolism. Practitioners should never forget that the body they deal with is the macroscopic manifestation of a tremendously complex biochemical machine and that as such metabolic features should always be considered at both the diagnostic and therapeutic stages.

Following the change of environmental conditions or external stimuli, organs and cells react and adapt in order to func-

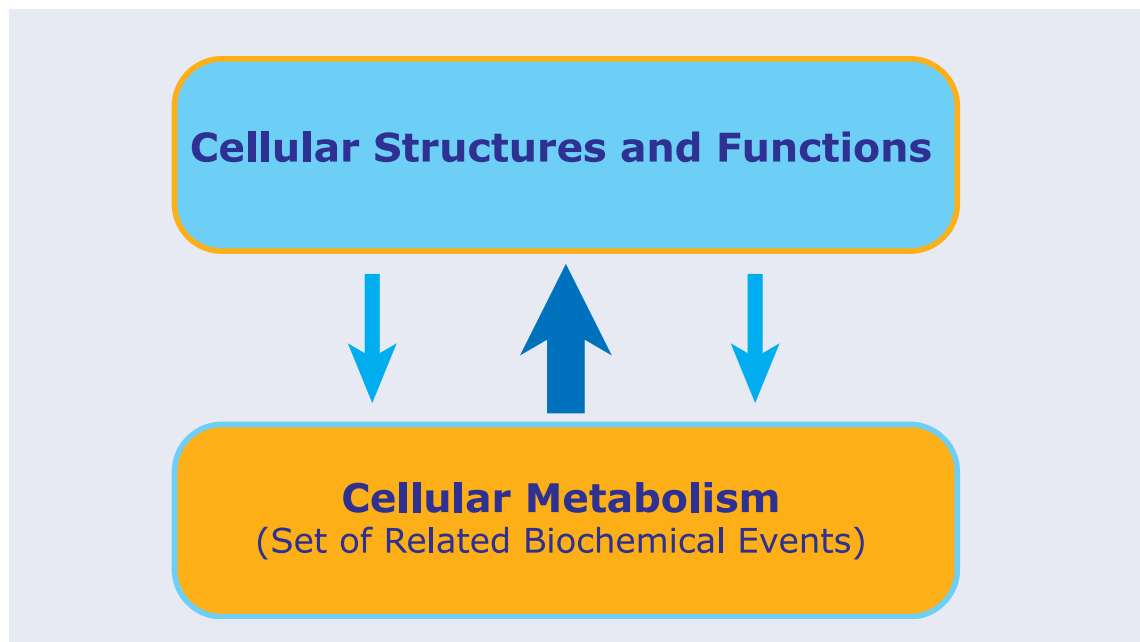
tion even when certain metabolic pathways<sup>1</sup> cannot be followed or are underexploited. As long as certain minimum requirements are met, the cell can survive and even carry out, at least in part, its proper function(s). This is due to an elaborate network of collateral pathways and control mechanisms which regulate and coordinate the rate of its reactions.

The schematic representation of the metabolic tracks resembles the map of a metro system. Just as any interruption along the line can be overcome by a detour of the train, cell metabolism most of the time will overcome a metabolic step not allowed by current conditions by following an alternative route to achieve its goal (e.g. the switch from aerobic to anaerobic metabolism for myocardial production of energy during angina pectoris). Unfortunately the longer the detour, the higher the cost: f.i. lower yield and higher

production of waste products (e.g. lactic acid). Conditions such as ischemia, inflammation, or suboptimal nutritional status of one or more nutrients may lead to substantial metabolic disruption. “This may result in cellular death and in an increase in DNA damage (and cancer), neuron decay (and cognitive dysfunction) or mitochondrial decay (and accelerated ageing and degenerative diseases)”<sup>2</sup>.

Cellular structures and functions are created and operated by metabolism which is in turn modulated by them (figure 1). Under normal conditions, metabolism induces modifications of cellular structures and functions within a “physiologic” range which allows the cell to carry out its “social” life. But when the changes go beyond these limits, cellular structures and functions may be modified to a point where irreversible cellular alterations and death (e.g. apoptosis) may occur and, most of

**Figure 1.** The structure-function/metabolism two way relationship.



**Table 1.** Lifespan through the ages<sup>5</sup>. It is noteworthy the reduction in average lifespan at birth between the upper Paleolithic (50 - 10 KY BC) and the Bronze Age (3,3–1,2 KY BC) i.e. when the transition from HG to F had virtually completely occurred<sup>28-38</sup>.

Humans by Era	Average Lifespan at Birth (years)
Upper paleolithic	33
Neolithic	20
Bronze age	18
Classical Greece	28
Classical Rome	28
Pre Columbia North America	25-30
Medieval Britain	25-30
Early 20° century	30-45
Current European average (27) 2006	75,8-82,0
Current world average	66,58

the time after a variable “silent” period of time, chronic and degenerative diseases, ageing, and increased metabolic demand conditions may show up with symptoms. This symptomatic phase is the crisis management area modern western medicine is extensively focused on<sup>3</sup>.

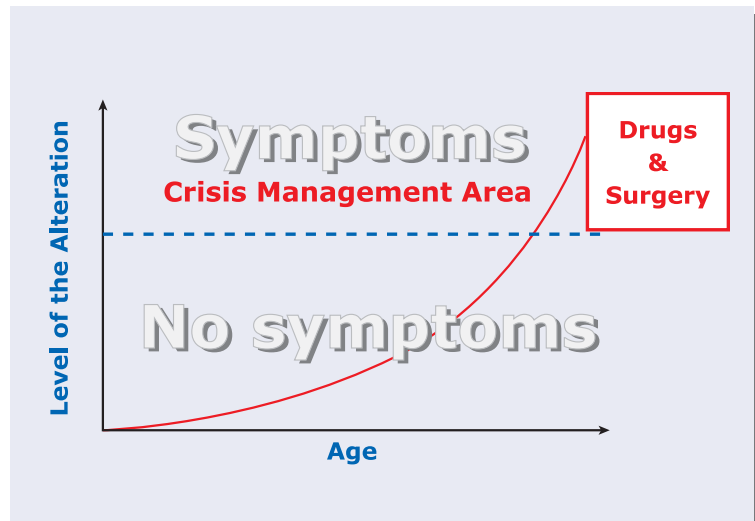
### Ageing, increased metabolic demand, and chronic and degenerative diseases

Amongst the many definitions of ageing given by a number of authors through the years, the one formulated by Strelher and Mildvan in 1960<sup>4</sup> is still probably among the best: “ageing is a process that is universal (all the members of a population of organisms will show it), progressive (the process is continuous and incremental rather than sudden), intrinsic (as opposed to death due to outside events), and degenerative (i.e. ageing is associated with increasing chances of mortality but also increasing level of morbidity)”.

Increased life expectancy is one of the most remarkable achievements of human mankind. Whilst it has been reliably estimated that life expectancy at birth in the prehistoric era was in the order of 25-35 years<sup>5</sup>, it has almost doubled in developed countries over the last century (from about 42 to around 80 in Western Europe) (table 1). Even though people are now li-

ving longer than ever before, a lot still remains to be achieved. It is becoming increasingly important to remain healthy and fit during these latter years in order to enjoy them as much as possible and decrease the healthcare bill. This is called compression of morbidity i.e. the reduction of either the extent of functional impairments or the duration of the morbid period

**Figure 2.** The long and silent story of chronic and degenerative diseases.



in human life. The importance of this issue cannot be overstated.

Several theories have been formulated to explain the mechanism of ageing. The so called "Green Theory of Aging"<sup>6</sup> currently seems to be the less unsatisfactory one in principle.

According to this theory ageing is the result of cumulative macromolecular damage due to the action of toxic metabolic byproducts (with reactive oxygen species being not the only player). As a consequence, a person's lifespan depends on the efficiency of either the removal of potentially damaging species or the repair of the damage caused by them. A central role in this is played by the capability of producing enough energy to carry out these effort consuming tasks and by the availability of all the micronutrients required. Unfortunately both of these factors decrease with aging and this is why metabolic support through targeted nutritional supplementation is more than a must in elderly people.

Chronic and degenerative diseases are based on metabolic (biochemical) alterations that run for long periods of time before they manifest symptoms (figure 2). They are the outcome of a gradual process of deterioration caused by the chronic imbalance in key metabolic mechanisms<sup>7</sup>. A typical instance is coronary artery disease: the atherosclerotic plaque doesn't develop overnight but it takes decades to develop to a point where symptoms appear. When medical attention is drawn by the problem it is time for drugs and surgery.

This imbalance may be due to an overload or undersupply of metabolic mechanisms. Even a

small reduction in required levels of selected nutrients (suboptimal nutritional level) after a prolonged period of time most frequently leads to various diseases<sup>8</sup>. Moreover, also diseases which are not primarily metabolic (e.g. infectious diseases and non pathologic bone fractures) are characterized by important metabolic features. The early stages of malnutrition (depletion) may not be evident and due to the lag of time elapsing between the instauration of the suboptimal nutritional status of one or more nutrients and the appearance of the symptoms of the chronic or degenerative disease, it may be difficult to connect the two events<sup>9</sup>.

Ideally degenerative processes should be stopped or, if this is not possible, their onset and progression delayed and slowed for as long as possible. It is becoming increasingly clear that proper nutrition plays a fundamental role in slowing and avoiding these degenerative processes<sup>10</sup>.

Any non chronic condition in which there is a call for increased metabolic performance of cellular functions (e.g. increased energy production, reactive oxygen species inactivation, immune system reaction etc.) can be defined as an acute increased metabolic demand condition (AIMDC).

Acute diseases, stress, increased physical effort and acute intoxications are conditions in which cellular metabolism has to augment its performance to support cellular/organ functions.

In order to allow cells and organs to successfully perform their function, the increased metabolic demand should be supported with targeted supplementation. This is even more so

for hydro soluble vitamins and any micro nutrients the body is not able to store or has limited capability to produce.

It should be noted that AIMDC may occur as both physiologic conditions (e.g. increased physical effort, pregnancy) or pathologic ones (acute infections, myocardial ischemia, etc.).

## Malnutrition

Malnutrition is often thought of as a problem to be found only in developing countries and when one thinks of this issue, the first image to come to mind is likely to be that of a starving child in a third world country. Although, this is obviously an example of a type of malnutrition which is unfortunately a severe problem in many developing countries, it should be noted that malnutrition is also widespread in developed countries<sup>11</sup>. Malnutrition in our society does not receive the attention it deserves and away from the clinical sphere, malnutrition in the community is particularly under-recognized. Solving this problem is not only a public health imperative, but would also yield important economic benefits. Malnutrition must be incorporated into the public health agenda<sup>12</sup>.

Although deficiency and depletion of one or more minerals, vitamins, or other micronutrients may arise from malabsorption of digested food, metabolic malfunction of one or more metabolic pathways, increased demand for one or more micronutrients or, eventually, be drug-induced, in many cases they are linked to an unbalanced diet. Considering the increasing levels of obesity and morbid obesity<sup>13</sup> it is clear that malnutrition is also

**Table 2.** Micronutrient deficiencies in individuals in the USA<sup>22</sup>.

Nutrient	Population group	RDA (µg)	Less than RDA consumption (%)	Less than half RDA consumption (%)
<i>Minerals</i>				
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
<i>Vitamins</i>				
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

commonplace in our own societies. It is common knowledge that the consequences of malnutrition and the body's reduced ability to defend itself from chronic and degenerative diseases (e.g. cancer, Alzheimer's disease and cardiovascular disease etc.) are extremely serious both for the individual and society as a whole<sup>14</sup>.

There is also evidence that nutritional deficits during development can have consequences later in life<sup>15</sup>. Since its proposal nearly 2 decades ago, the hypothesis that suboptimal maternal and fetal nutrition can have a profound and sustained effect on the health of a person in later life has gained support from human epidemiologic and animal studies<sup>16</sup>.

A study of subjects conceived during the Dutch famine, a five month period of extreme food shortage during the winter of 1944 - 1945 in World War II, showed that those exposed to famine had a higher cumulative incidence and an earlier onset of coronary artery disease than unexposed persons<sup>17</sup>.

A number of people are at higher risk of malnutrition. Listed below are several predisposing conditions/lifestyles<sup>18</sup>:

- dieters
- smokers
- alcoholics
- athletes
- tanning fanatics
- vegans and vegetarians
- women taking the contraceptive pill
- chronic and acute diseases
- traumatic injuries and surgery
- pregnant or lactating mothers
- postmenopausal women
- elderly people.

However in actual fact, unless under a comprehensive supplementation program, everybody in developed countries is practically malnourished.

Human diet requires both macronutrients, the main source of calories, and micronutrients (approx. 40 essential minerals, vitamins, and other biochemicals), which are required for virtually all metabolic and developmental processes<sup>19</sup>.

Modern diet contains significant

reduced quantities of micronutrients, (table 2) and even a so called "balanced or varied diet" that provides adequate calories is very likely unable to supply appropriate levels of the required micronutrients. This is also known as the empty calories phenomenon<sup>18</sup>.

For example, in the United States the regular diet is abundant in carbohydrates and fats but deficient in micronutrients (i.e., energy dense and nutrient poor)<sup>20</sup> and hence even in this country there is commonly inadequate intake of some vitamins and minerals.

The table 3 is related to a survey carried out by the US department of agriculture in 1993<sup>21</sup>.

The above percentages are calculated on the recommended daily allowance (RDA), which means that the actual depletion is far worse than what shown by the survey.

In fact RDAs are very unlikely to be sufficient to supply the correct amount of micronutrients we need daily as they were developed having in mind

**Table 3.** Percentage of vitamin depleted population in the USA<sup>21</sup>.

Vitamin	A	E	C	B1	B2	B3	B4	B6	B12
% of population depleted	55	68	37	32	31	27	34	54	17

the prevention of deficiency diseases and were not meant to point out the correct amounts that need to be assumed daily to properly support metabolism.

A survey carried out in the UK has shown that as for vitamin C, about 95% of the population has a daily intake which doesn't protect them from chronic and degenerative diseases vitamin C depletion related (e.g. cardiovascular diseases, some types of cancer). Remarkably also people taking a vitamin C supplement based on the current RDA (60 mg) are members of this depleted 95%. A different concept has been developed as for the amounts

of micronutrients to be considered the correct daily intake: it is called Suggested Optimal Daily Amount (SODA) which in the case of vitamin C has been calculated to be around 500 mg per day<sup>18</sup>.

**Deficiency and Depletion**

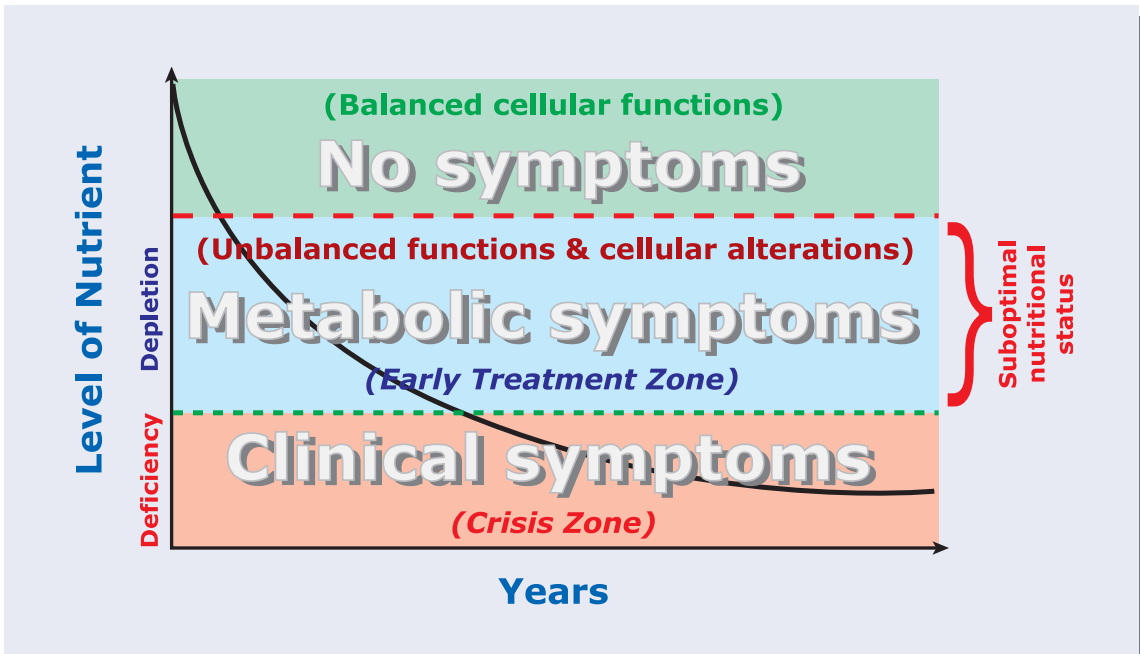
As there is a big difference between these two conditions, particularly from the standpoint of the consequences, any possible confusion should carefully be avoided.

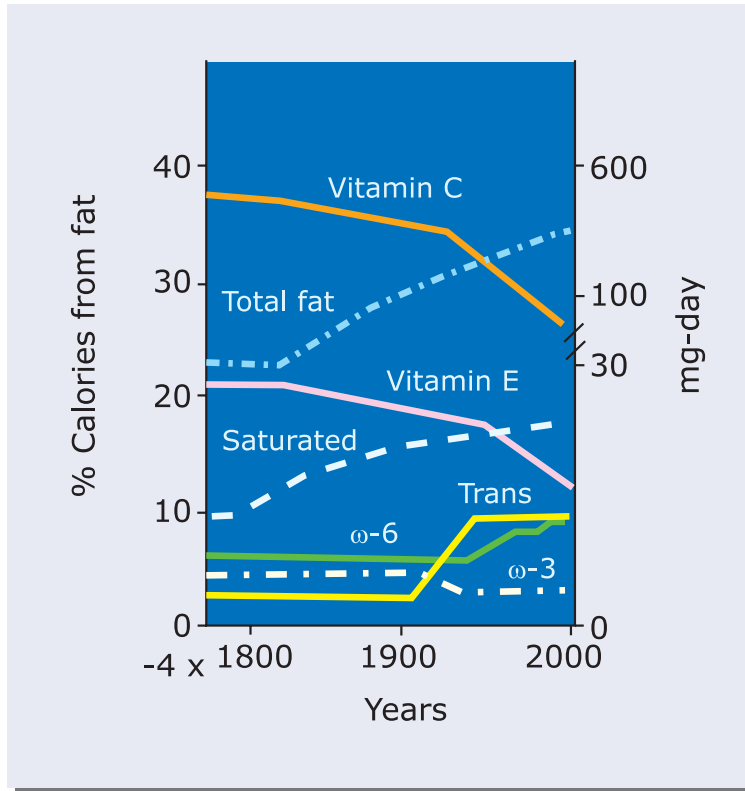
Deficiency occurs when the level of micronutrients is sufficiently low to cause clinical symptoms of a related disease. Scurvy secondary to a prolonged period of inadequate vita-

min C intake is a perfect example of deficiency.

Depletion on the other hand occurs when the level of a certain nutrient is sufficiently reduced to negatively influence metabolism but not low enough to induce immediate clinical symptoms of its shortage. Much before the onset of clinical symptoms, the depletion of micronutrients causes cell and organ damage<sup>22</sup> and increases the risk of chronic disease, such as coronary artery disease and cancer. Depletion is significantly more common than deficiency and can be transitory, depending on the circumstances (e.g. before pregnancy, when there is a higher de-

**Figure 3.** Depletion of a nutrient & symptoms.



**Figure 4.** Diet evolution during the last last two centuries<sup>26</sup>.

mand for folate to prevent neural tube defects).

Figure 3 points out how during the very early stages of micronutrient depletion usually there are no clinical symptoms. As the depletion advances, cellular functions become altered and unbalanced, and metabolic symptoms appear<sup>23</sup>. This phase represents the so called suboptimal nutrition status area and metabolic (early) treatment, using relatively simple measures, should be implemented. When lower levels of the micronutrient are maintained over a period of years, clinical symptoms usually develop. This is a “crisis zone”: treatment of the condition at this stage will be much more complicated and the usual response of medicine is drugs and/or surgery. Deficiency and depletion should be detected on the ba-

sis of the specific nutrients involved and the search for them should take into consideration their function and their kinetics. For example deficiency of L-carnitine or omega 3 fatty acids are best detected in the muscle or red blood cells (RBCs) respectively rather than in serum.

The suboptimal intake of micronutrients<sup>20</sup> is often associated with caloric excess<sup>24</sup> and may be the norm among the obese and contribute to the pathologies associated with obesity<sup>19</sup>.

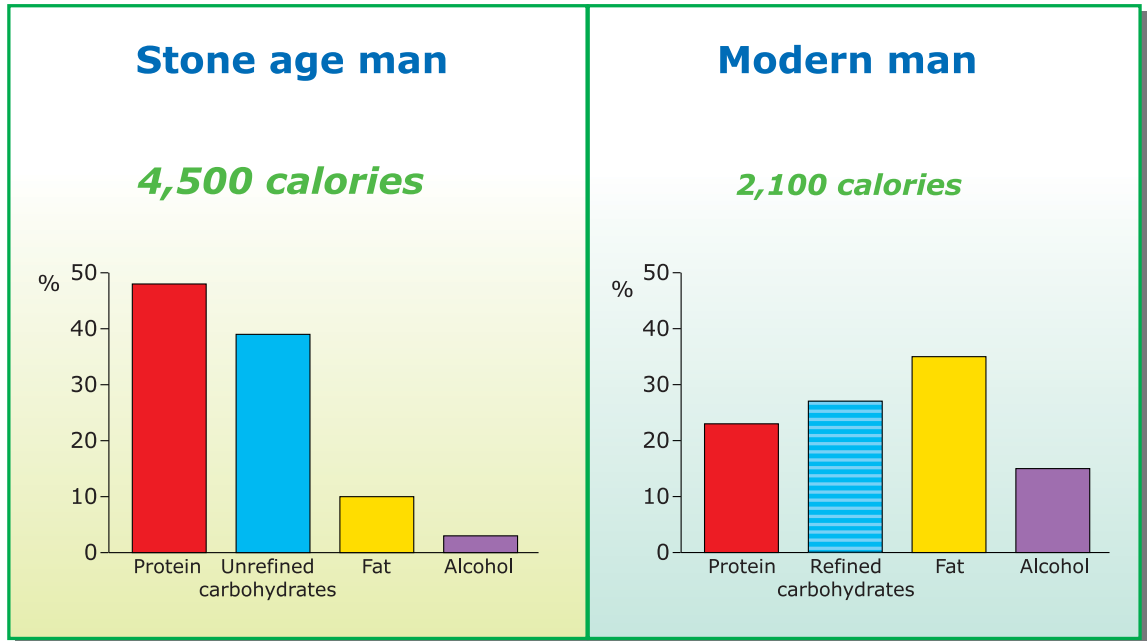
It should be stressed that in developed countries the suboptimal nutritional status of selected nutrients is not only relevant to obese, diabetic, or elderly people, but, due to the poverty of micronutrients in the food, involves most of the population<sup>25</sup>.

## Nutritional changes in human diet throughout the ages and planned duration of human life

Two major changes have occurred in human diet during the last 10,000 years which may be held responsible for several paramount deleterious effects on human health.

The first of them happened between 10,000 and 3,000 years B.C. During this period humans went from being predominantly hunter-gatherers to farmers. This change was advantageous in that smaller areas of land could sustain an increasingly numerous population, however it also had a negative impact on the health of our ancestors and consequently on ours. As the shift from hunter-gatherers to farmers progressed and the diet was restricted to a limited number of vegetable species and animals, the nutrient variety in food decreased in a significant manner. In fact hunter-gatherers would draw 65% of their calories (in the range of 4,000-4,500 a day) from fruit and vegetables of which they would eat about 100 different species. Farmers would only get 20% of their calories from fruit and vegetables and would largely base their caloric intake on cereals which are poorer in micronutrients. Also the amount of meat they could eat was lower in comparison to hunter-gatherers. With lower levels of nutrients in the food it is perfectly logical that diet would not have had the same nutritional value as before the shift.

Among the most significant consequences reported were decreased life expectancy (in Illinois River Valley it dropped from 26 y to 19 y) and decrea-

**Figure 5.** Amount and source (%) of calories in human diet at the Stone Age and today<sup>18</sup>.

sed height (in the territories corresponding to current Greece and Turkey, men and women went from 175 cm and 165 cm to 160 cm and 150 cm respectively). Other notable points included farmers suffering from rickets, scurvy, anaemia, dental cavities (hunter gatherers had very few unrefined carbohydrates in their diet), malnutrition, parasitic diseases and infectious diseases (leprosy, tuberculosis, malaria etc.) to a much greater extent than hunter gatherers.

The second major change in human diet in developed countries has occurred during the last 100 hundred years.

During the last century the amount of total fat, saturated fat, trans fatty acids, and omega 6 has increased whilst omega 3 and micronutrients such as vitamin E and C have decreased<sup>26</sup>. In the same time the availability of calories has risen, thus making it very difficult for

anybody to stay away from unnecessary energy, and fulfill the increased requirements of micronutrients related to aging and increased metabolic demand conditions.

As a matter of fact if we compare the diet of the cave man with that of a contemporary individual, it is easy to notice not only the fall in caloric intake (from 4.000-4,500 to 2,100 a day), but also the substantial change in the percentage of the different nutrients: more fat and alcohol, less proteins, and a remarkable shift from unrefined to refined carbohydrates. Figure 5 represents the daily intake of calories and the type of foods eaten from the Stone Age until today<sup>18</sup>.

Current western diet is characterized by several nutritional defects which include excessive glycaemic load, increased omega6 to omega3 ratio, increased saturated fatty acids, reduced intake of fiber, increased

sodium to potassium balance, excessive amount of daily calories, and an increased amount of alcohol<sup>27</sup>.

Coupling this with the virtual steadiness of human genes over the same period of time, leads us to the conclusion that we are literally running a car on a fuel that was not designed for it.

Furthermore, we expect the car to run smoothly until the end of its life span, which has almost doubled over the last century in developed countries.

In Europe, 110 years ago the average life expectancy was 40-43 years whereas it is currently between 75,8 (men) and 82 (women) years. Even though the aging process is well underway by the age of 40, we are expecting to live twice as long as before, remaining fit and healthy during the second half of our life.

As a matter of fact it is not unreasonable to assume that na-



tural selection didn't "design" our body to live until the ages that we reach nowadays in developed countries. In other words, more than half of our life span was not planned by Mother Nature. This is also due to the fact that whatever genetic defect shows after we have reached the reproductive age, has no influence on our reproductive capability and may consequently be transmitted to the next generation.

Until natural selection has been effectively operating, mankind's life expectancy has been in an order of magnitude much shorter than the life span we currently enjoy in territories like Europe, the USA and most developed areas of the world (table 1).

It is a fact that the increased availability of food (calories), hygiene, and medicine have progressively raised the number

of years a person may expect to live, but it is also true that the second half of our life is not necessarily the healthier one.

### Nutrients and the consequences of their deficiencies

Inadequate nutrition has been linked to an increased risk of many diseases, including cancer, heart disease and diabetes<sup>19</sup>. The subtle metabolic damage caused by micronutrient deficiency could result in an increase in DNA damage (and cancer), neuron decay (and cognitive dysfunction) or mitochondrial decay (and accelerated ageing and degenerative diseases)<sup>2</sup>.

Mitochondrial dysfunction seems to play a major role in aging and associated degenerative diseases, including cancer

and neural decay<sup>39</sup>. It has been reported that increased amounts of oxidant by-products are generated by the mitochondria of old rats compared with that of young rats. In comparison with those from younger rats, mitochondria from older rats also have decreased membrane potential, respiratory control ratio, cellular oxygen consumption, and cardiolipin (a key lipid found only in mitochondria)<sup>40</sup>. Oxidative damage to DNA, RNA, proteins and lipids in mitochondrial membranes adds to the mitochondrial decay, leading to functional decline of not only the mitochondria but also cells, tissues and eventually organs such as the brain with associated loss of ambulatory activity<sup>41</sup>.

The World Health Organization defines elderly as "persons of 60 years of age or older"<sup>42</sup>. In 2009 the percentage of the

**Table 4.** Potential contributors to nutritional problems in the elderly.

Physical factors	Social and psychological factors
Reduced total energy needs	Depression
Declining absorptive and metabolic capacities	Loneliness
Chronic disease	Social isolation
Anorexia	Bereavement
Changes in tastes/odour perception	Loss of interest in food or cooking
Poor dentition	Mental disorders
Reduced salivary flow	Food faddism
Dysphagia	Socioeconomic factors
Lack of exercise	Low income
Physical disability (restricting the capacity to purchase, cook, or eat a varied diet)	Inadequate cooking or storage facilities
Drug-nutrient interactions	Poor nutrition knowledge
Side effects of drugs (anorexia, nausea, altered taste)	Lack of transportation
Restrictive diets	Shopping difficulties
Alcoholism losses	Cooking practices resulting in nutrient
	Inadequate cooking skills (men)

total worldwide population aged 60 years or over was 11%. This value is expected to rise to 22% by 2050<sup>43</sup>.

Furthermore, the population 80 years or older is projected to more than triple and the number of centenarians is expected to increase 15-fold from 1999 to 2050<sup>44</sup>.

The fact that more people than ever before are surviving to old age demonstrates the noteworthy accomplishments in health and social development. With these achievements come further responsibilities and challenges of supporting these individuals, knowing that older people are ill more often than young people and their illnesses and ailments are usually longer lasting.

The prevalence of malnutrition is particularly high in older people and unfortunately it is very likely to be much higher than the values officially reported (over 10% of the population aged 65 years and above). Furthermore older people are less likely to recover from malnutrition<sup>12</sup>.

### Healthy life expectancy

Disability-adjusted life expectancy (DALE) which summarizes the expected number of years to be lived in what might be termed the equivalent of “full health” is the principle measure of population health used by the WHO. To calculate DALE, the years of ill-health are weighted according to severity and subtracted from the expected overall life expectancy to give the equivalent years of healthy life<sup>42</sup>.

The separation of life expectancy into equivalent years of good health and years of lost good health provides a

useful insight into the provision of health services and nutritional support to extend healthy life expectancies by reducing the years of disability<sup>45</sup>. There is an abundance of scientific evidence that demonstrates that modifiable environmental, lifestyle and nutritional factors are prominent determinants of health and life expectancy<sup>46-49</sup>.

### Factors influencing adequate nutrition in older people

There are many physical, mental, social and environmental changes that take place with ageing, such that normal daily activities are hampered to some extent because of chronic ill health (table 4).

Nutritional deficiencies in the elderly impact not only at an individual level in terms of health status, wellbeing and life expectancy but also at the society level since the dramatic increases in the age of populations and societies places and will place a significant burden on the healthcare systems and economies of all countries. Over half of the costs of malnutrition are expended on people over the age of 65 years. Many of the social and economic causes of malnutrition, such as poverty, poor mobility, depression and social isolation, are more prevalent among older people<sup>12</sup>.

Addressing malnutrition in older people in the community requires an inter-sectorial approach. The practice of screening for malnutrition in the community by health, social care and community service providers and professionals must be embedded. The awareness of malnutrition amongst older people, their families

and the public at large must be raised. Awareness of malnutrition in older people remains insufficient not only amongst the general public and older people, but amongst many healthcare professionals as well<sup>12</sup>. There is a wealth of evidence that demonstrates that proper nutrition and specific nutrients play a major role in maintaining and enhancing physical and mental performance as well as delaying the onset of chronic diseases and the process of aging<sup>50-52</sup>.

The overall nutrient density of the diet is particularly important in the elderly<sup>53</sup>. In addition to the poverty of micronutrients in food, the suboptimal nutritional status of selected nutrients is worsened by the reality of what people choose to eat daily.

A particularly important point is drug-induced micronutrient depletion. Anticonvulsants, diuretics, gastric acid suppressants, glucocorticoids, biguanides, statins and methotrexate are all examples of drugs which interfere with body absorption or use of micronutrients such as vitamin D, calcium, folate, magnesium, thiamin, vitamin B12, coenzyme Q10 etc. Unfortunately very few doctors bear this in mind when evaluating the impact of drug treatment especially in the elderly<sup>19</sup>. This is one more reason why individuals of all ages, and in particular older people, have to include food supplements in their diet in order to meet their needs for micronutrients.

Increases in healthcare expenditure will outpace economic growth in many countries. Bearing this in mind, the wider use of food supplements would be a cost-efficient method of providing nutritional support and

favorably modulating the age-related decline in most organ functions and the development and progression of many chronic diseases.

Research in elderly populations has documented the nutritional vulnerability of older people in developing and developed countries, even under relatively affluent circumstances. Ensuring micronutrient sufficiency by means of selection of nutrient-dense foods, foods with added nutrients and food supplements becomes of even greater importance in the ageing population<sup>45</sup>.

### Triage theory

Many micronutrient deficiencies are associated with chromosome breaks and cancer in humans, cause DNA damage in rodents or human cells in culture, and, where assayed, cause early senescence<sup>54-56</sup>. It has been proposed that DNA damage and late onset diseases are consequences of a triage allocation mechanism developed during evolution to cope with episodic nutrient shortages. During periods of micronutrient shortage, some functions of micronutrients are restricted and as a consequence insidious changes accumulate and increase the risk of diseases of aging<sup>2,57</sup>.

Living creatures have always required approximately 15 metals/minerals for their metabolism, which are distributed very unevenly throughout the Earth. Therefore, episodic shortages of these as well as for vitamins and other essential micronutrients were probably common. It is known that natural selection favours short-term survival at the expense of long-term health when they are in conflict.

In 2006 Ames hypothesized that as the scarcity of a micronutrient increases, and after homeostatic adjustments, such as induction of transport proteins, a triage mechanism for allocating scarce micronutrients is activated that favours short-term survival at the expense of long-term health, in part through an adjustment of the binding affinity of each protein for its required micronutrient<sup>19</sup>. In essence, the functions required for short-term survival take precedence over all those that are less essential.

The consequences of such triage would be evident at all levels, e.g.

- in metabolic reactions – enzymes involved in ATP synthesis would be favoured over DNA-repair enzymes
- in cells - erythrocytes would be favoured over leukocytes
- in organs - the heart would be favoured over the liver.

Validation of this theory would suggest that it may be necessary to optimize intake of micronutrients according to the needs of the most dispensable organ or cells in order to maximize longevity and retard cancer and other degenerative diseases of aging.

Physiological triage is already well recognised: when there is inadequate oxygen delivery to tissues the vital organ function is maintained by intrinsic neurohormonal compensatory mechanisms resulting in distribution of organ blood flow primarily to the heart, brain and adrenal glands and away from other 'nonvital organs'<sup>58</sup>. Similarly, in cases of micronutrient deficiency, organs such as the liver lose their micronutrients before other more vital organs such as the brain<sup>59</sup>.

### Metabolic Targets

Micronutrient supplementation can target various metabolic functions that are affected by micronutrient depletion. These targets include:

- energy production
- defense from oxidative stress
- defense from osmotic stress
- cellular membrane building and maintenance
- apoptosis
- eicosanoids formation.

Energy production in conditions of micronutrient depletion may be decreased or associated with increased production of free radicals. These are atoms, molecules or ions containing one or more unpaired electrons which play important biochemical roles. Two forms of free radicals, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are particularly relevant when considering human biochemistry. These two species are by-products of mitochondria-catalyzed electron transport reactions and inflammation. They are also generated by irradiation (UV light, x-rays and gamma-rays), metal catalyzed reactions and are present as atmospheric pollutants. In low concentrations they play physiological roles in important functions such as defense against infectious agents, cellular signaling systems and induction of mitogenic response. However, in high concentrations they have harmful effects including peroxidation of DNA, proteins, lipids and cell membranes consequently causing damage to cellular structures and functions and leading to cell death.

Osmotic stress due to the depletion of micronutrients is caused by the inhibition of the transport of substrates and co-

factors as well as cell swelling and bursting. Micronutrient depletion also causes alteration of cell membrane functions and can alter the rate of apoptosis. By targeting and acting synergistically on these specific metabolic steps, micro-nutrient supplementation supports and improves cell functions and preserves cellular structures.

When considering targets for therapy it is important to reflect upon the fact that patients are individuals and as with all therapies specific supplementation needs to be implemented.

Micronutrient supplementation needs to be targeted according to the needs of the respective individual. This will vary case by case based on their age, genetic predisposition, socioeconomic background, lifestyle and other risk factors for disease.

Suboptimal levels of nutrients are not only due to malnutrition: in actual fact toxins, stress, disease, aging and other factors may determine an increased demand for certain nutrients. Ultimately not only basic cellular functions such as energy production and antioxidant capacity may be severely impaired, but also cell structures may be affected by the suboptimal nutritional level of one or more nutrients.

The only way to fix this is targeted supplementation as the alterations due to suboptimal levels of micronutrients cannot be fixed by drugs, whilst eating a varied diet (including the Mediterranean diet) is highly likely unable to supply the required amounts of micronutrients.

## The Metabolic Approach

The metabolic approach implemented through micronutrien-

ts supplementation is aimed both at the early treatment area during which there are no clinical symptoms, and the crisis management area, when symptoms are present and drug therapy/surgery are part of the management plan.

The metabolic approach allows the implementation of the early treatment option and offers an additional tool for managing disease as it is based on the administration of metabolic compounds (i.e. metabolic substrates, intermediates and coenzymes – i.e. carnitines, coenzyme Q10, omega-3 FA, alpha lipoic acid etc.) and their synergistic combinations. It is focused on correcting specific metabolic steps that are altered in aging, disease or increased metabolic demand conditions in order to restore and preserve cell structure and functions. By achieving this the approach aims to delay aging and delay/stop the development and the progression of chronic and degenerative diseases.

The objectives of The Metabolic Approach are:

- to delay/avoid the onset of chronic/degenerative diseases (e.g. cancer, cardiovascular diseases, Alzheimer's disease and Parkinson's disease etc.);
- to improve quality of life particularly in the second part of it;
- to improve response to drugs and surgery;
- to improve prognosis of acute diseases at any age;
- to improve the function of organs and apparatus of the body.

## Crisis management

Most of modern medicine currently adopts a crisis manage-

ment approach to disease. This approach, undoubtedly effective in many conditions, is extensively focused on symptoms and naturally leans towards the use of more and more expensive technology and potent pharmaceuticals which also appeal to patients very much. Another characteristic of modern medicine is the use of drugs usually concentrated on a single “trigger” trying to deal with a complex phenomenon in a simplistic way, thus very often failing to appreciate the complexity of biologic phenomena. Although modern medicine has improved the management of emergencies and acute ailments, consequently leading to increased duration and improved quality of life, it implies huge costs and focuses relatively little on chronic and degenerative diseases. This approach may play a role in the occurrence of the mental bias against the use, integration and evaluation of a non primary pharmacological approach in healthcare.

Chronic and degenerative diseases are complex phenomena based on cellular and organ alterations which develop over long periods of time (silent development time) before manifesting clinical symptoms (figure 4). In fact symptoms are usually a late event in this type of processes and when they appear, and the condition enters the crisis management area, the underlying metabolic changes have been there a long time and cellular and organ alterations have been well established. These features become so important that they must be dealt with in an appropriate and timely manner even in diseases which are not primarily metabolic. In fact the

very nature of biologic phenomena calls for an approach to complexity which is far from the point of view of classic pharmacology.

### The Early Treatment Option

Taking a burning building as an example of a crisis management condition, keeping the match box out of the reach of children is an example of prevention: impeding the occurrence of a particular event. An example of early treatment in the same scenario would be blowing out the flame of the burning match held by the kid as soon as possible before it sets the whole house on fire: the process is already underway, however a relatively simple, early intervention can avoid serious consequences that would otherwise occur.

The key to early treatment is making the right move at the right time. The “we will cross that bridge when we come to it” attitude is unfortunately common within society and healthcare and the widespread mentality is that if there are no symptoms, or even if symptoms are present but they do not impact too much on daily life, then there is no need to take action.

What needs to be stressed is that our patients and ourselves are already on the bridge and moreover we need to realize it as soon as possible. Even before the onset of clinical symptoms there are already early alterations in metabolic processes and early treatment is required<sup>19</sup>.

Early treatment consists of the administration of targeted combinations of metabolic compounds (e.g. vitamins, antioxidants, omega 3FA, etc.). It needs to be recognized that early metabolic changes may already

be occurring and they need to be dealt with and corrected while they are still at an early stage. The longer these dysfunctional processes are left uncorrected, the more detrimental they are to overall health and wellbeing and the more difficult they become to correct.

The implementation of early treatment of these metabolic alterations is the key to delaying the deterioration of cellular structure and functioning. This consequently could delay the onset of symptoms of chronic and degenerative diseases, the aging process and improve the body's ability to respond to acute diseases.

Furthermore the early treatment approach takes care of the core of the problems in due time. In chronic and degenerative diseases, while patients are on their way to developing symptoms, every effort should be made in order to avoid this or to prolong the symptom free period for as long as possible.

In 2000 an eight-week double-blind, placebo controlled trial involving 80 American adults aged between 50 and 87 years consuming an adequate and fortified diet was carried out in order to determine whether a daily multivitamin/mineral supplement could improve micronutrient status, plasma antioxidant capacity and cytokine production<sup>60</sup>. Participants were excluded from the study if they had used dietary supplements regularly in the three months prior to screening. During the treatment period participants received either supplementation in the form of a multivitamin/mineral preparation formulated at about 100% Daily Value (DV) or placebo. Fasting blood samples were taken at baseline and also on days 49 and 56. Baseli-

ne characteristics were comparable between the two groups and there were no significant differences in terms of plasma micronutrient concentrations at baseline.

Following the eight week treatment period, participants in the supplement group had significant elevations in the plasma status of vitamins D [25(OH)D] and E ( $\alpha$ -tocopherol) ( $p < 0.01$ ) of 30% and 21% respectively. No significant changes in fat-soluble vitamin status were detected in the placebo group. Supplementation reduced the prevalence of low vitamin D status from 7% to 0% and suboptimal  $\alpha$ -tocopherol from 73% to 49%.

Supplemented participants also showed significant improvement in the plasma concentrations of vitamins B<sub>6</sub>, B<sub>12</sub>, C, riboflavin, pyridoxal phosphate and folate. No changes in either plasma or red blood cell glutathione peroxidase and in oxygen radical absorbance capacity (ORAC) were found in either the supplement or placebo group. No significant changes in water-soluble vitamin status were found in the placebo group.

Supplementation reduced the prevalence of suboptimal plasma vitamin C, folate, vitamin B<sub>12</sub> and vitamin B<sub>6</sub> concentrations.

Since the dietary intake of the vitamins did not change during the study, the reported changes in vitamin status can be attributed to the supplement. The results reported in this study are in line with other studies involving comparable populations with similarly formulated multivitamin preparations<sup>61,62</sup>. Not only did the multivitamin reduce the prevalence of poor nutrient status, it also increa-

sed several vitamins into a more optimal range relevant to reducing the risk of chronic disease. Improving the status of folate, vitamins B<sub>6</sub> and B<sub>12</sub> is effective in reducing plasma homocysteine<sup>63</sup> which, in-turn is related to a reduced risk for cardiovascular disease<sup>64</sup>. Moreover, low levels of plasma folate, B<sub>6</sub> and B<sub>12</sub>, independent of the plasma homocysteine concentration, are associated with an increased risk for heart disease<sup>65,66</sup>. The study concluded that supplementation with a multivitamin supplement can improve micronutrient status in healthy, older Americans to levels above those obtained with a fortified diet. This improvement in nutritional status reduces the prevalence of suboptimal plasma vitamin concentrations and will shift blood levels of key nutrients into ranges associated with reduced risk for several chronic diseases.

## Conclusions

It is clear that suboptimal nutrition is a problem even in developed societies and there is growing evidence that this has wide ranging implications for the development of chronic and degenerative diseases as well as on the outcome of acute diseases.

Support is also building for the targeted administration of metabolic substrates and intermediates in order to delay the onset of the symptoms related to these conditions.

The metabolic approach based on targeted dietary supplementation is based on sound rationale and scientific literature and should be added to the armamentarium by which modern day medical practice promotes health and sustains the wellbeing of patients at all stages of life. Not only does the approach offer benefits for individual patients but also, in socioeconomic terms, for society as a whole.

A key advantage of this approach is that it allows for supplementation of metabolic compounds at a much earlier stage than the point at which medical and surgical therapies may be implemented. To optimize long-term health and wellbeing it is necessary to consider the future and rectify any underlying metabolic problems as early as possible. In many conditions it is no longer acceptable to wait until symptoms appear before dealing with the underlying metabolic alterations. Furthermore, when clinical symptoms occur, the patient might be at the

point where the treatment has to be focused on “damage limitation”. The advent of genomics, proteomics and, most of all, metabolomics is enabling us to take a deeper and deeper look into the future health status of our patients thus allowing a full implementation of the early treatment option.

Unfortunately it is all too easy to find scientific literature that reports the poor levels of nutrition within our societies. There is no doubt that there is a link between inadequate intake of micronutrients, metabolic imbalance and many clinical symptoms and diseases. This problem is ready and waiting to be tackled and with so much at stake we too must be ready to take action.

The simple return to the Paleolithic diet doesn't seem to be a good strategy. The second part of our current life expectancy is a period which was not originally foreseen by natural selection and as such it should be wisely planned way in advance from the nutritional standpoint. If nothing is ventured then nothing will be gained, but by taking the opportunities that we are being offered there is a chance to make a huge impact on the sustained health and wellbeing of individual patients and also on society as a whole. **TiM**

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