VOLUME 3 • ISSUE 3

ADVANCES IN ORTHOMOLECULAR RESEARCH

Anti-Aging

Health: How Times Have Changed

Benegene: Unlocking the Secrets

Resveratrol: Life Extension and Health Benefits

Mitochondria: Maintaining the Power Plant

research-driven botanical integrative orthomolecular breakthrough

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Health is one of our most basic needs. It is said that it is the greatest possession, the first liberty, the basis for hope, and the ultimate blessing. Life expectancy has increased steadily over the past century with the advent of treatments for infectious diseases, which used to be the leading cause of death worldwide. This has resulted in a rise in chronic diseases which has also led to initiatives encouraging healthy lifestyles. Contrary to infectious diseases, non communicable diseases are typically irreversible. Their prevention is therefore essential and understanding why such diseases arise has become the cornerstone to the future of healthcare.

Too often, health is not truly appreciated until it is lost. The average Canadian family spends more on transportation, clothing, recreation, insurance and furniture than on health. In fact, Canadians spend almost as much on tobacco and alcohol as they do on their health.[1] Not surprisingly, our health is often left wanting. The average Canadian employee misses seven days of work per year due to sickness and every week, 8.3% of Canadian workers are unexpectedly absent from work for at least a day.[2] In 2005, there were over two million hospitalizations in Canada - 8.4 hospitalizations per 100 residents.[3] In the United States, there are more nurses than waiters, cleaners, truck drivers or elementary school teachers.[4]

Rank	Symptom	Million Visits
1.	Cough:	22.40
2.	Sore throat:	17.50
3.	Skin Rash:	13.37
4.	Vision disorders:	12.97
5.	Knee pain:	12.53
6.	Back aches:	12.46
7.	Gastrointestinal distress:	12.28
8.	Ear infections:	11.29
9.	Hypertension:	10.40
10.	Depression:	10.04

Symptoms prompting the most US doctors' visits in 2000.[5]

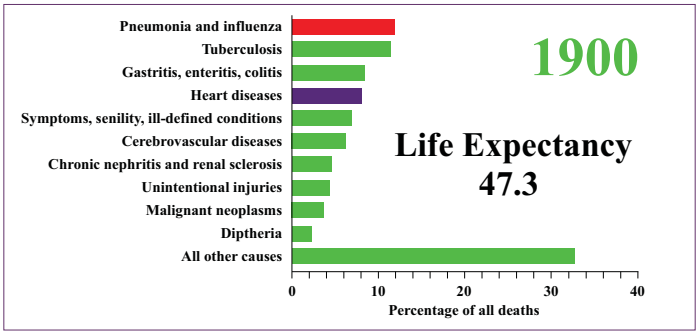
Cardiovascular disease:	64 million	
Hypertension:	50 million	
High cholesterol:	37 million	
Type 2 diabetes:	11 million	
Overweight:	65%	of US population aged 20 or more
Osteopenia:	39.65%	of women over 50
Osteoporosis:	7.2%	of women over 50

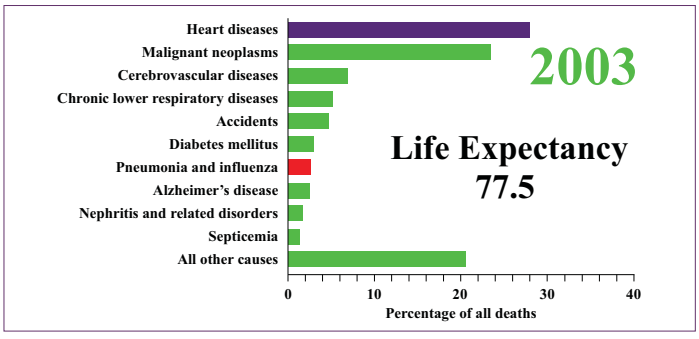
Chronic disease incidence in the United States:[6]

The things we worry about...

We wear seatbelts, hold handrails, buy cars with airbags, put on helmets and install smoke detectors in our homes because we all want to feel safe. We are scared of airplanes, public speaking, sharks, heights, terrorists, the avian flu, natural disasters, thunder, bees, snakes and mad cow disease... The problem is that on the grand scheme of things, accidents are not a major threat to us when they are compared to the leading causes of death.

We worry about the wrong things. Accidents are unpredictable and largely out of our control but chronic diseases which are the leading cause of death in North America are preventable.





Causes of death in the United States in 1900 and 2003.

Why do we become ill?

The traditional medical approach has been to look at how a disease develops. For instance, we know that heart attacks are caused by the occlusion of blood flow to the heart... but why does this occur? Understanding why diseases develop is essential to their prevention.

Life is only concerned with the survival of the species. This means that traits which promote the continuance of life are "naturally selected". As life evolved, the traits that favored successful reproduction and survival were passed on to future generations. Disadvantageous traits were selected against and eventually disappeared. Changes, although very slow, continue to occur in our physiology. For example, trends towards smaller molars and lower bone densities have been noticed in contemporary humans.[7] Present day Europeans and Asians have bones that are 20 to 30% lighter than their ancestors from 30 000 years ago.[8] The reason behind such a change is simple: bigger teeth and stronger bones offer no advantage because we do not need to chew as much and are less likely to suffer from bone fractures in our youth than our ancestors.

Shadows from the Past

Even though evolution can be driven by random mutations, there are no coincidences. The genes we possess today have gone through a use-it-or lose-it screening process. The diseases and illnesses we suffer from today can be understood by comparing what nature dictated in the past versus how we live today.

It is also important to realize that a gene has a multitude of effects and a specific disease may prevent another. There are several examples of such disease preventing other disease interactions.[9] For instance, elevated uric acid levels in the blood as seen in gout provide additional antioxidant protection (uric acid is an antioxidant)[10] and prevent the development of MS.[11] Sickle cell disease protects against malaria.[12] Cystic fibrosis reduces the likelihood of contracting tuberculosis[13] and severe diarrhea.[14] Phenylketonuria and type 1 diabetes may reduce the probability of miscarriages.[15] Every disease, anatomical structure and physiological process can be rationalized by examining the costs and the benefits associated with it.

Interfering with complex disease interactions and mechanisms which appear to be counterproductive may not be in our best interest. For instance, diarrhea is a protective mechanism that helps to eliminate toxins and bacteria from the gastrointestinal tract. Patients given anti-diarrheal medication take longer to recover.[16] Similarly, fever optimizes the immune response[17] and anti-fever medications prolong illness in subjects infected with influenza A.[18] Aspirin and acetaminophen increase nasal symptoms and lengthen the period of viral shedding (and therefore contagiousness) in rhinovirus-infected individuals.[19] This suggests that the usefulness of these treatments should carefully be assessed. Evolution dictates that such mechanisms have been selected because they are beneficial. Although anti-fever and anti-diarrheal medications provide relief while we are sick, they also appear to keep us sick longer.[20]

The disease of aging

Natural selection favors genes that maximize reproduction even if they compromise health and longevity.[21] Aging is eventually fatal for all of us but if we did not age, probability dictates that half of us would live to 693 and 13 percent of the population would live to be 2000 years of age.[22] This would lead to a phenomenal increase in the population which would not be able to sustain itself.[23] This explains the high birth rates seen in populations with high mortality rates and vice versa. The other important cause driving the aging process revolves around the costs and benefits that are associated with specific genes. Genes have a multitude of effects and those that are beneficial early in life may cause disease later on.[24]

Aging is biologically controlled, with strong evidence that oxidation, glycation and methylation are closely associated with premature disease and the acceleration of the aging process.[25-33] This explains why healthier lifestyles increase health span and longevity.[34,35]

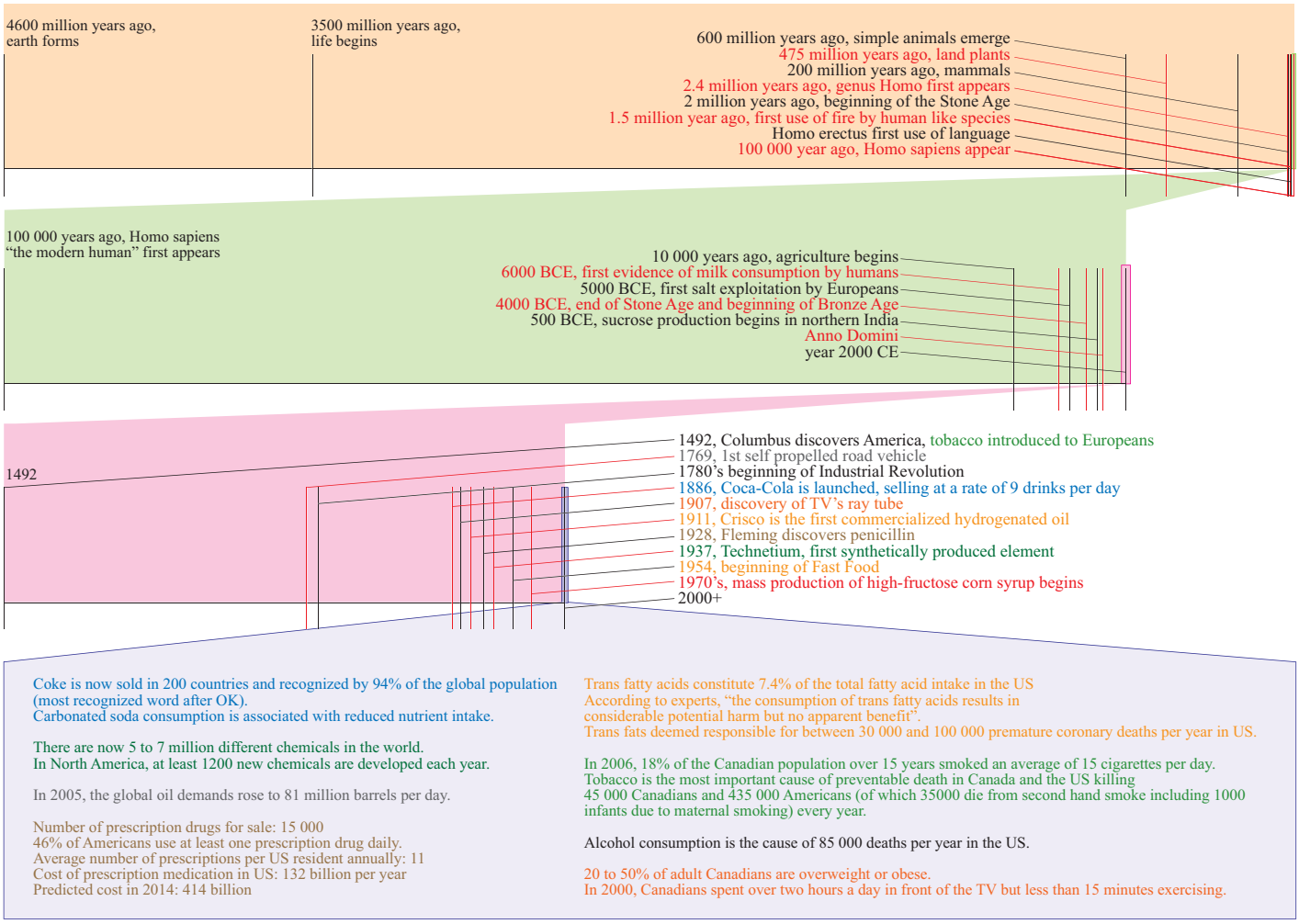
When maladaptation becomes the norm

Humans have thrived because of our seemingly infinite ability to adapt. Unfortunately, our relatively recent ability to modify the environment has changed our surroundings at a pace that is far too rapid for adaptation. This has resulted in our present state of health. Although we live longer than ever before and enjoy comforts previously unimaginable, we are also plagued by degenerative disorders and for the first time in recorded history, upcoming generations may well see shorter life expectancies.[36]

According to evolutionary medicine, disease is caused by maladaptation - an event that occurs when an organism does not possess the genes suited for its environment. For example, sickle cell, which protects against malaria,[37] is of little benefit in countries where malaria is not present. In such cases, sickle cell is detrimental and represents a maladaptation.[38]

If the environment changes rapidly, a large segment of the population becomes maladapted. A good illustration of this phenomenon is myopia. Can you imagine the disadvantage associated with shortsightedness prior to the availability of corrective lenses? The evolutionary selection against such a trait would be immense. The prevalence of myopia reaches close to 40% in some developed countries[39] but is rarely seen in hunter gatherers.[40]

The evolution of life and disease



A study done in Singapore showed that as the education level increases, so does the incidence of myopia. The study demonstrated that in young men with no formal education, the prevalence of myopia was 15.4% but reached 65.1% in university graduates.[41] This phenomenon is probably caused by a simple mechanism which stimulates the growth of the eye to ensure that vision remains focused. Close work would therefore lead to the formation of a visual focal point that is adapted for close work at the detriment of far sight. Myopia is a clear example of the health impact associated with maladaptation.

The problem is that evolution occurs over thousands of years and until recently our ancestors were hunters and gatherers.[42] Unfortunately, our modern technological advances have changed our environment so rapidly that we are left with genetic traits that are suitable for a very different environment.[43]

Our diet - past and present

For hunter-gatherer populations, the securing of food would have been the main purpose of life - starvation, malnutrition and irregular nutrition would have been common in such populations.[44] In today's developed world, changes in food staples and food processing have lead to a diet that is very different than that of our ancestors.

There are several consequences to these changes, one of which is an increase in the glycemic load. The glycemic load represents the effect of food on blood sugar and therefore insulin levels in our body. Carbohydrates, especially refined grains and sugars, have high glycemic loads and their consumption eventually leads to insulin resistance, a significant factor in the development of several diseases of civilization such as obesity, cardiovascular diseases, diabetes, hypertension and elevated blood lipid levels.[52] Obesity alone is responsible for an estimated 350 000 deaths per year in the United States.[53]

Major changes to human diet in the recent past:[45-50]

Highly refined grain flours, unavailable 200 years ago, now contribute 85.3% of the cereal and 20% of the total energy of the average US diet.

Fiber content has decreased from an estimated 42.5 g per day to 15.5 g per day.

Refined sugar consumption, estimated at 2 kg per person per year (from honey) in hunter-gatherers, has climbed from 6.8 kg in 1815 to 54.5 kg per person per year in England today.

90% of the salt intake in the US diet is added to the food supply. With refined salt, sodium consumption went from ~768 mg per day to ~4000 mg per day in Americans.

From 1909 to 1999, salad and cooking oil consumption increased by 130% in the United States, shortening (lard) consumption increased by 136% and margarine by 410%.

Animal fat consumption has increased from 8% of total calories in the 1960s to 13% in the 1990s.

In the United States, the greatest health threat to the population comes from the development of chronic diseases related to the diet.[51]

The type of fat present in the diet is also crucial for health and probably more important than the amount of total fat present in the diet.[54,55] Unsaturated fats are beneficial whereas saturated and trans-fats are detrimental, especially when consumed in excess. The ratio of omega-6 to omega-3 oils is also important for health.[56] This ratio has now reached a 10-20:1 proportion whereas ancestral diets probably approached a more reasonable 1-3:1 ratio.[57-59]

Another serious consequence of eating more refined foods is a reduction of the nutrient density of the diet. Refined sugars are devoid of any nutrients and constitute empty calories. Refined vegetable oils also provide little nutritional value. Together, refined oils and carbohydrates contribute 36.2% of the energy in the average US diet.[60] The consequences of a reduction of the nutrient density of the diet have lead to inadequate nutrient intakes in a large proportion of the population (see figure 1).

72.1% of the energy in the US diet comes from food which would not have contributed to the diet of our ancestors.[62] This has lead to diets that contain fewer amounts of antioxidants, fiber, vitamins and phytochemicals compared to hunter-gatherer diets.[63] It is probable that our preagricultural diets contained two to ten times more micronutrients.[64]

Supplementation - a modern day necessity

Given the limitations of the 21st century lifestyle and the current dietary nutritional content, good quality nutritional supplements can be used to meet nutrient requirements and to improve the nutrient concentration of the diet. As already mentioned, the nutrient density of our diet has suffered from the addition of refined food products such as sugar and oils. This problem is further aggravated by modern farming techniques which have also depleted the nutrient supply. (See figure 1)

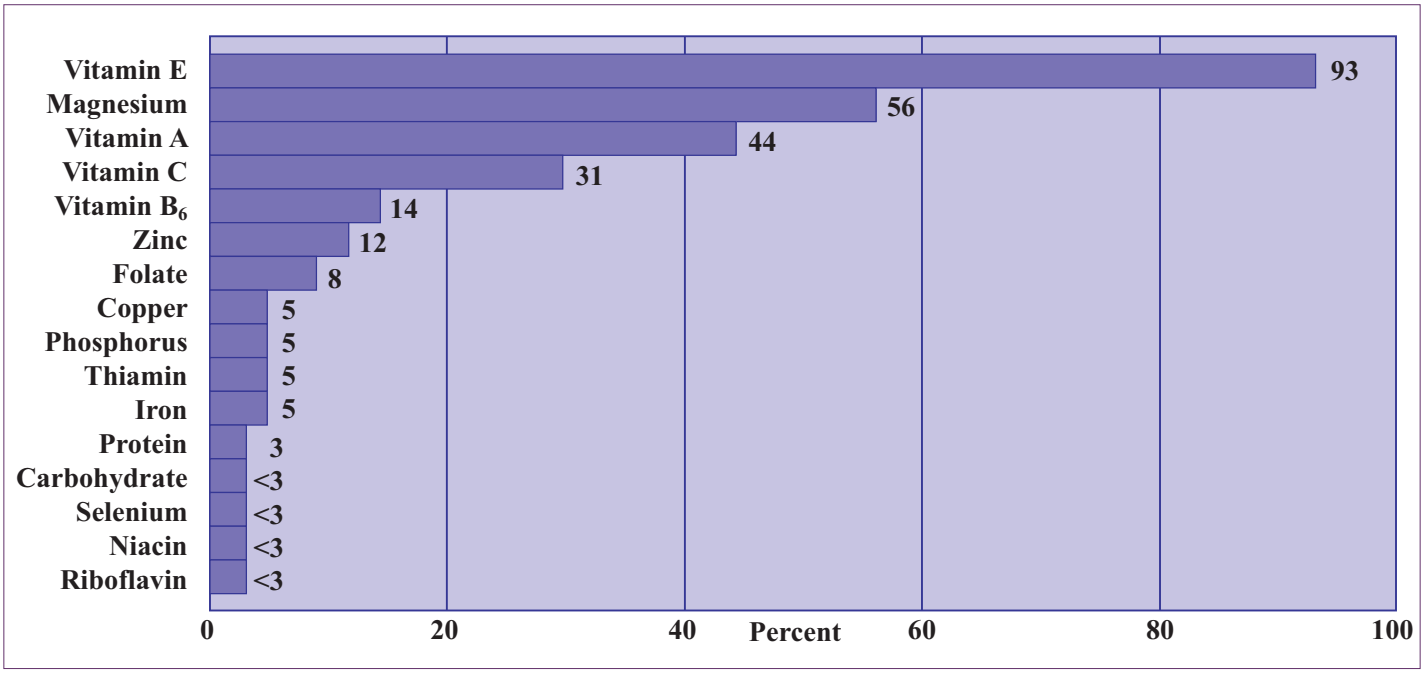


Figure 1: Percentage of Americans with Inadequate Intakes from Food Based on Estimated Average Requirements.[61]

Percentage change in the nutrient content of fruits and vegetables in Canada between 1951 and 1999

Apple	20.0	-55.3	-41.1	16	-75.0	-66.7	-30.0
Banana	-23.8	-41.7	-81.2	-13.0	0	-100.0	-1.4
Broccoli	-62.8	-33.9	-55.9	-10.1	-40.0	-42.9	-2.7
Onion	-37.5	-52.9	-100.0	-54.8	56.9	-41.2	135.3
Potato	-27.5	-58.6	-100.0	-57.4	-14.6	-50.0	44.9

source: Health Canada, compiled by Jeffrey Christian

Based on population studies and examinations of our dietary past, there is strong evidence suggesting that you may not be able to get all the nutrients you need from the food you eat. Reductions in the nutrient density of the diet has left the majority of the United States population with nutrient intakes not meeting the recommended intake levels, vitamin E being the most blatant example with an estimated 93% of the population below the Estimated Average Requirements (EAR) (see Holistic International, Volume 1 Issue 4 available online at www.aor.ca for more information on the importance vitamin E). This is a clear indication that dietary changes must be recommended and that fortification and supplementation are currently needed to fill this nutritional gap.

Humans have thrived because of our seemingly infinite ability to adapt. Unfortunately, our relatively recent ability to modify the environment has changed our surroundings at a pace that is far too rapid for adaptation. This has resulted in our present state of health. Although we live longer than ever before and enjoy comforts previously unimaginable, we are also plagued by degenerative disorders and for the first time in recorded history, upcoming generations may well see shorter life expectancies.[66]

Health is simple. How we should be taking care of ourselves is based on how we have lived for thousands of years, which means that we should exercise more, eat fresh and unprocessed food, supplement our diet and maintain a healthy weight. We already know this and still 20% of us smoke and the vast majority of us do not meet our basic nutritional needs. Hopefully understanding why we must take better care of our health will give us the will to act accordingly. Whereas in the past, infectious agents posed the greatest threat, you are now the largest determinant of your health. You must stand up for yourself or endure the consequences and risk loosing your greatest possession.

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Unlocking the secrets of Anti-aging

3-carboxy-3-oxopropanoic acid and the NAD+/NADH ratio

3-carboxy-3-oxopropanoic acid (3C3-OXO) mimics calorie restriction. It focuses on increasing and decreasing the activity of genes in a similar manner that calorie restriction changes the activity of the genes. Over 350 genes are expressed in a manner similar to calorie restriction, resulting in an astonishing increase in average and maximal lifespan, weight reduction, and glucose reduction in multi-species animal tests. Human clinical trials have confirmed both reduction in glucose levels and improved uptake in glucose without negative side effects. This simple modification to metabolism has major implications for cancer prevention and treatment, diabetes prevention and management, atherosclerosis, macular degeneration, and neurological decay including Alzheimer's and Parkinson's.

Benefits of modifying cellular metabolism to produce calorie-restricted conditions.

The benefits of calorie restriction have been studied for over 70 years. Calorie Restriction (CR) is the reduction in the overall amount of calories (by 30 to 50%) while maintaining proper nutrition. It has been the only proven method to extend the maximal lifespan of mammals. CR has been shown to cause major beneficial shifts in health and metabolism on a wide range of organisms, from the single cell to very complex (including humans). The wide range of success of CR indicates that the process of life extension is based on similar effects observed between species, and occurs on the molecular level of individual cells.

Mice that receive adequate nutrition but a reduction in calories have delays in the onset of many age related diseases including cancer, diabetes, and Alzheimer's [Hursting, 2003]. A reduced calorie diet also leads to an increase in average and maximal lifespan. This data strongly shows that humans will also live longer [Fontana, 2004 Ingram, 2006].

The benefits of calorie restriction are due to changes within each cell that forms the gene expression and include those involved in:

- immune response
- protein turnover
- protein synthesis

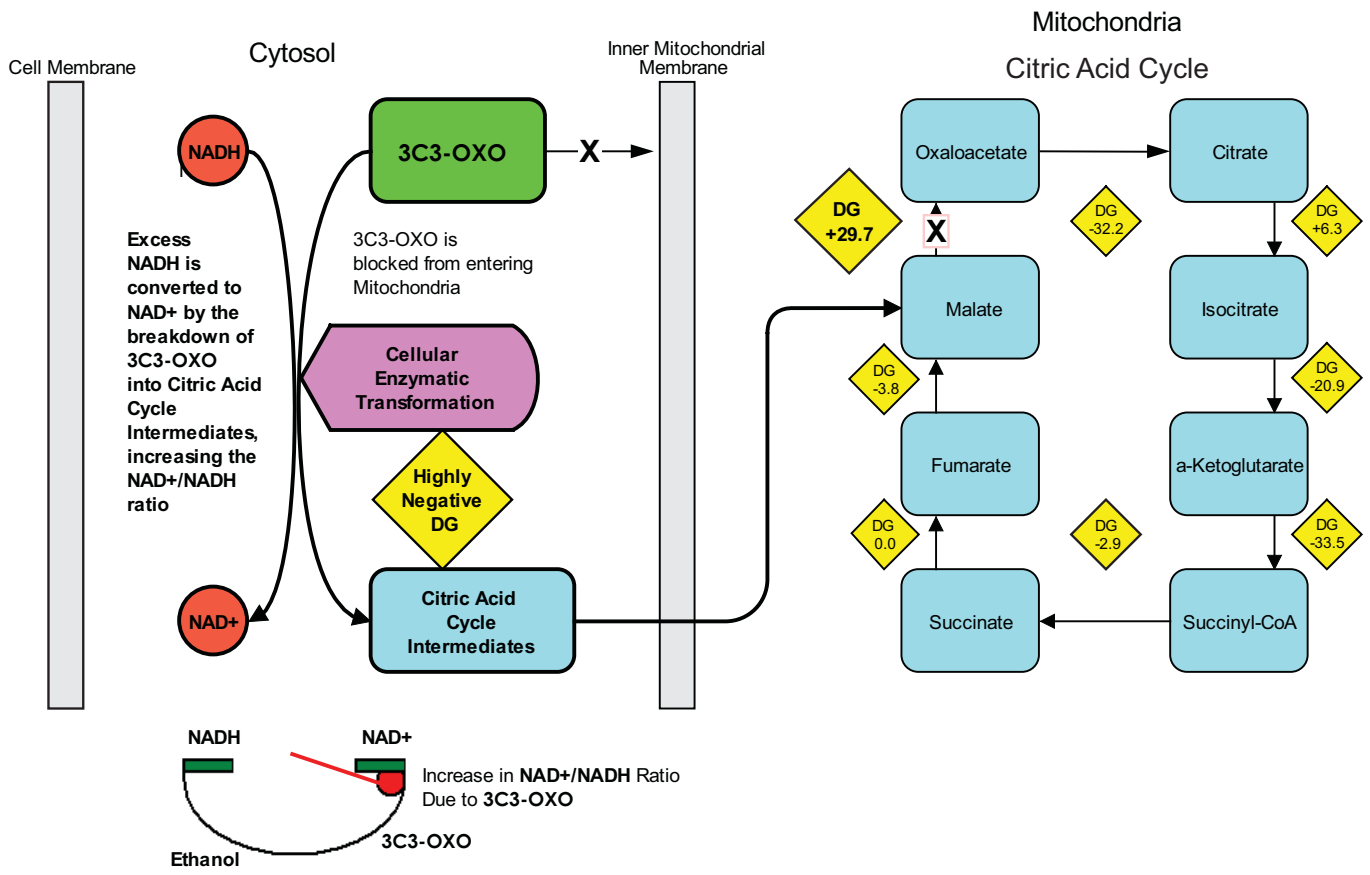
[Lee, 2004]. Masternak et. al. [2004] show that genes related to insulin and insulin growth factor 1 (IGF1) are altered including PPAR-alfa, a gene that is suggested to play an important role in metabolic control, accumulation and preservation of fat storage cells.

The activity of FOXO genes have also been shown to change under caloric restriction [Furuyama 2002, Daitoku, 2004]. "FOXO factors may act as tumor suppressor genes and it is the loss of their function that may be the pivotal event in tumorigenesis" [Arden, 2006, Greer 2005]. "These same FOXO genes may play a role in preventing DNA damage by inducing expression of genes important in the detoxification of reactive oxygen species (ROS)" [Arden, 2006]. Studies of humans undergoing CR for 3 to 15 years have shown reduced risk for atherosclerosis along with reductions in fasting glucose, fasting insulin, Hs-CRP levels, systolic and diastolic blood pressure, triglycerides, total cholesterol, and LDL cholesterol as compared to equivalent age-matched controls [Ingram, 2006].

How does 3C3-OXO work?

3C3-OXO mimics what happens during calorie restriction, and modifies the cellular energy pathways to activate multiple genes already shown to be beneficial. The key mechanism of action of 3C3-OXO is changing the ratio of Nicotinamide Adenine Dinucleotide (NAD+) and the reduced version, NADH. 3C3-OXO increases the NAD+ to NADH ratio by the action of a biological diode. When added to the cell, 3C3-OXO converts NADH into NAD+ in the cytosol and ends as a simple member of the citric acid cycle family of compounds. The inner mitochondrial membrane acts as the diode mechanism for the reaction, not allowing 3C3-OXO into the mitochondria, but forcing the reaction converting NADH into NAD+ in the cytosol. This changes the electrical state in the cytosol. The increased NAD+/NADH ratio/change in electrical state is the same critical signaling mechanism as seen in calorie restriction [Lin 2004], and results in the increased expression of many beneficial genes. These beneficial genes allow an increase in average and maximal lifespan, increased overall health, reduction in blood glucose levels and reductions in weight in laboratory animals. Clinical trials in humans have documented the reduction in blood glucose levels, but there is not sufficient information at this time to show if there will be an increase in maximal human lifespan-we should have this data in about 130 years. In the meantime, we look at the successful increases in lifespan of multiple short lived species to document the possible effect of 3C3-OXO on humans.

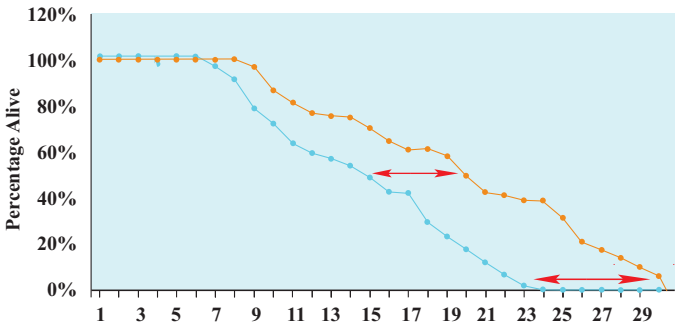
The effects of 3C3-OXO as a biological diode and the citric acid cycle



3C3-OXO increases the NAD+/NADH ratio. The increased ratio is a change in electrical state, and acts as a cellular signaling mechanism for the increase in beneficial gene expression. Supplied extra-cellular 3C3-OXO penetrates the cell membrane but cannot penetrate the Mitochondrial membrane, which acts as the diode mechanism. 3C3-OXO converts to Citric Acid Cycle Intermediates in the cytosol through existing cytosol enzymes. The produced Citric Acid Cycle Intermediates diffuse into the Mitochondria, but are only slowly converted by the Citric Acid Cycle due to the high positive delta G (shown as DG) of the reaction. The Biological Diode created keeps the NAD+/NADH ratio higher than would normally occur, mimicking the internal cellular conditions of Caloric Restriction. The mimic of calorie restriction conditions increases beneficial gene expression and clinically increases Health span and Lifespan in laboratory test animals.

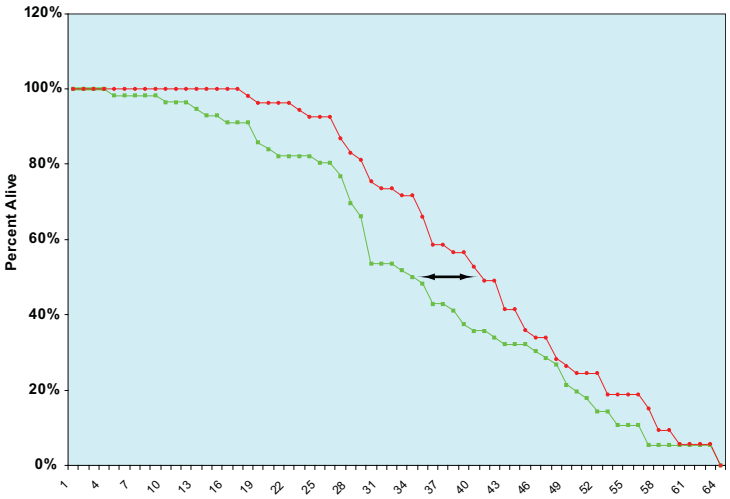
3C3-OXO increases average and maximal lifespan in multiple species by up to 40%

Investigation on biological diode compounds, and 3C3-OXO in particular, initially started on a well known worm, *Caenorhabditis elegans*. This worm is selected for many studies because its genetics are rather well understood. In adding 3C3-OXO to the agar on which the worms live, researchers observed a dose dependant increase in lifespan. The more 3C3-OXO added, the longer the life of the worms. This was an important test, as one of the major properties of the gene changes seen in calorie restricted animals is the ability to increase lifespan. Once worms reach adulthood, their cells do not divide - so the only way for them to live longer is on a cellular level, allowing each cell to live longer.



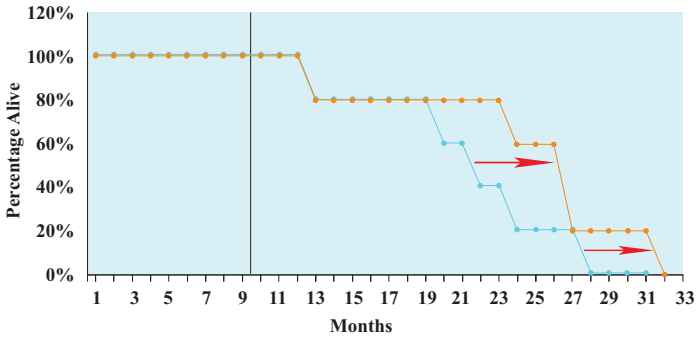
C. elegans (worms) live 36% longer than the control group when 3C3-OXO is added to the agar.

After testing the compound on worms, research was moved on to the fruit fly, which is a more complicated animal. Again, 3C3-OXO supplementation in the fly food increased lifespan. It was interesting to note that in flys, an increase in maximal lifespan was seen when the flys were placed under stress, The maximal lifesapan was increased by over 100% as compared to the control group. This is primarily because stress killed off the control flies, and did not greatly affect the 3C3-OXO flys.



Fruit flies live 20% longer than the control group when 3C3-OXO is added to their food.

Worms and flies are great, but what about complex animals such as mammals? We share 98% of our DNA with mice, and the metabolic pathways are particularly similar from mice to humans. A common breed of laboratory mice, C57BL/6, was selected for the longevity experiments, and started with older males. Males were used because they typically live shorter lifespans than females. Again, in pilot testing, an increase in average and maximal lifespan was seen when 3C3-OXO was added to the mouse food. Even though the 3C3-OXO supplement was started 1/3 of the way through their lifespan, the mice still lived 25% longer than the control group. Both groups were allowed to eat unrestricted amounts of food. Maximal lifespan was increased by 14%. Not only was lifespan increased, but heath span was also increased. The mice on 3C3-OXO showed less signs of inflammation, reduced incidence of spine curvature, and reduction in hair graying. 3C3-OXO is now being tested on a larger group of mice.



Supplementing mice with 3C3-OXO lead to an increase of 23% in average lifespan, and an increase in maximal lifespan of 14%. Mice were started on 3C3-OXO in their 9th month. The increase in average "Residual" lifespan was 39%, similar to what can be achieved with calorie restriction.

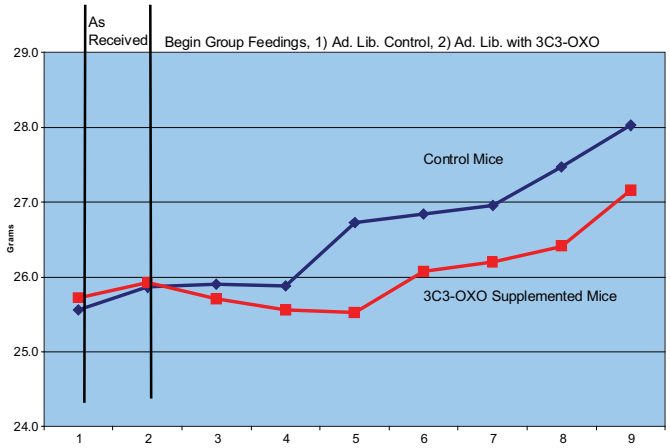
3C3-OXO interacts with genes to reduce fat content

Adding 3C3-OXO to the food of mice decreased the weight gain of C57BL/6 mice allowed to eat unrestricted amounts of food, as compared to the control group. The genes that control the storage and mobilization of fat tissue were altered reducing the overall weight gain. The effect took approximately 3 weeks to be measurable. Reduction in fat content is a positive health benefit also seen in calorie restricted mice.

3C3-OXO lowers blood glucose levels and improves glucose uptake

In a clinical trial, diabetic patients ranging from 15 to 95 years old were given 3C3-OXO for 30 to 45 days. Fasting levels of glucose in both type 1 and type 2 diabetic patients were decreased by an average of 23.7% in the trial. No negative side effects were noted. Glucose uptake by tissues was also increased in diabetic patients by 299%. Glucose uptake in non-diabetic patients was improved by 180%. The reduction of glucose in the bloodstream ties very well to a calorie restricted state. Interestingly, Kitamura [2005] showed that FOXO1 (one of the genes upregulated by both calorie restriction and 3C3-OXO) protects against pancreatic beta cell failure, which again ties to the genomic response of both calorie restriction and 3C3-OXO supplementation from the animal models. In addition, Nyengaard [2004] stated that the free NADH in the cytosol "accelerates the onset and progression of diabetic retinopathy (and other complications of diabetes)". 3C3-OXO specifically targets cytosolic NADH and converts it into NAD+.

It is also important to note that lower glucose levels will automatically lead to lower levels of Advanced Glycation Endproducts (AGEs), which may also lead to longer lifespan.



Adding 3C3-OXO to the food of mice decreased the weight gain of C57BL/6 mice allowed to eat unrestricted amounts of food, as compared to the control group.

3C3-OXO mimics the genomic profile of calorie restricted animals

Researchers examined the genomic profile of the mice fed the 3C3-OXO supplement as compared with mice that were fed a calorie restricted diet, and then compared both groups to a control group. Gene chips were used to look at the expression of over 20,000 genes in liver tissue. Based on the gene chip data, it was observed that the calorie restricted group had 1,763 genes change in activity as compared to the control group, a very good indication that diet does change the expression of genes. This change in gene expression has been seen in other calorie restricted studies [Cao 2001, Lee, 2004, Masternek 2004]. In the 3C3-OXO supplemented group, which were allowed to eat freely, 765 genes were changed in expression levels as compared to the control group. Because of the pooled data, the most interesting genes were genes that showed changes in expression in both the calorie restricted group and the 3C3-OXO supplemented group. 363 genes were shown in both groups to have "moved away" from the expression of the control group. These 363 genes are involved in lifespan extension, as is proved by the 3C3-OXO supplemented group living longer (average and maximal lifespan extension). The 363 genes were in some cases increased in activity, and in other cases decreased in activity. Comparison of the direction of the changes in gene activity between the 3C3-OXO supplemented mice and the calorie restricted mice (as compared with the control group), indicated a positive overlap of 98%. When an expression change of 1.7 was applied to the data to rule out false positives, the data showed a 100% positive overlap in gene expression change direction for both groups away from the control group.

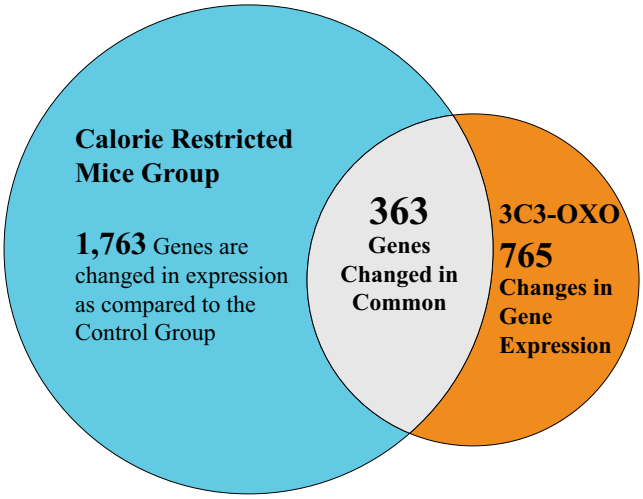
Implications for Cancer Prevention

Calorie restriction is one of the most effective means to delay the onset of cancer [Hursting, 2003]. The tie between genes expressed under calorie restriction that increase lifespan and decrease cancer proliferation has been hypothesized by Anisimov [2003]. Further to that hypothesis, it was shown that increased activation

Gene Symbol	Gene Title	Affy-matrix Gene Number	Change in Gene Expression Calorie Restricted to Control	Change in Gene Expression 3C3-OXO to Control	Gene function
Foxo1	forkhead box A1	2891	30% Increase	40% Increase	regulation of transcription, DNA-dependent // inferred from electronic annotation
Foxo3	forkhead box A3	13370	100% Increase	70% Increase	cell glucose homeostasis // inferred from mutant phenotype // regulation of transcription, DNA-dependent // inferred from mutant phenotype // cellular response to starvation // inferred from mutant phenotype
Foxq1	forkhead box Q1	6994	110% Increase	210% Increase	regulation of transcription, DNA-dependent // inferred from electronic annotation
Foxq1	forkhead box Q1	30006	190% Increase	220% Increase	regulation of transcription, DNA-dependent // inferred from electronic annotation

As can be seen by the table of FOXO genes that have changed, the mimic effect between mice that have 3C3-OXO supplemented diets and mice that are calorie restricted is very strong, providing a strong potential between the proven cancer reduction rates in calorie restricted animals and 3C3-OXO supplemented animals. Further work on this potential is being researched.

of the longevity gene FOXO3 encoded a protein to prevent cancer and predict a better outcome for breast cancer patients [Hung, 2004]. More recently, Yamamura [2006] showed that FOXO3 is needed to induce apoptosis (programmed cell death) in gastric cancer cells. Pinkston, et. al. [2006] documented that genes that increase the lifespan of C. elegans (worms) also inhibit tumor growth. Arden [2006] reviews the FOXO genes for potential new therapeutic targets for a broad spectrum of cancers. Her review indicated that FOXO1 is a tumor suppressor gene. She also reports that "FOXO3 can override IkB stimulation of the cell cycle progression, proliferation and tumorigenesis in mice, further supporting FOXO3 as a candidate tumor suppressor gene."



The researchers of 3C3-OXO were excited to see the FOXO type genes were part of the 363 genes that increased in expression levels (as compared to the control group) in both the calorie restricted group and the 3C3-OXO supplemented group. (See Table)

3C3-OXO defines a new class of calorie restriction mimetic compounds, shown to have similar benefits to calorie restriction- an increase lifespan in all species tested to date, reduced glucose levels, improved glucose uptake by tissues, increased stress resistance and produces similar genomic changes. 3C3-OXO is composed of metabolites already existing in every cell of the human body- just more is added to effect a biological diode action with the mitochondria. The components of 3C3-OXO are found in excess in red apples, perhaps leading to the saying, "An apple a day....."

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Resveratrol is a polyphenolic compound found in various berries (cranberry, blueberry, grapes) and herbs. Studies with trans-resveratrol have reported a diverse range of benefits in the areas of heart health, immunity and inflammation. Research has also revealed that trans-resveratrol mimics the biological longevity effects of a calorie-restricted diet.

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Life Extension and Health Benefits of Resveratrol

There is no doubt that many among us, in the context of dinner-party banter or some other setting conducive to the transfer of anecdotal wisdom, have heard that a glass of wine a day is good for your health. 'A healthy heart and a long life' is usually the jist of this particular nugget of scientifically secular populist enlightenment. The long life that is inferred is attributable to a substance that the scientifically observant elite have identified as resveratrol, a phytonutrient originating -in this case - in the vinyards. Resveratrol, in turn, elicits this wondrous effect largely by mimicking many of the biological chain of events seen in the practice of Calorie Restriction Optimum Nutrition (CRON), or simply Caloric Restriction.

Caloric Restriction is the only tried and tested method of increasing life span in numerous and diverse species, from yeast, worms, fruit flies, spiders, rodents, all the way up to primates. Anecdotally, the ancient rishis and yogis of India were reputed to live long beyond their years because of dietary restrictions. In 1945, Cornell University researcher Clive McCay reported that caloric restricted mice lived considerably longer than matched controls (mice that ate a normal number of calories).

Calorie restriction generally refers to an approximately 40% reduction in caloric intake, usually accompanied by a normal, maintenance level of nutrients. Calorie restriction dramatically extends life span, both average and maximum. Moreover, there is an improvement in the health status of an organism from reduction in the various biological markers of disease e.g. blood lipids, glucose, triglycerides, insulin levels, inflammatory cytokines (ultra sensitive C Reactive Protein and NF-kappa-B), free radicals, advanced glycating end products (AGE's), advanced lipolyting end products (ALE's) etc. The reduction in these bio-markers translates into lower incidence of diabetes, obesity, cholesterol, high blood pressure, cardiovascular disease, arthritis, cataracts, neurological diseases and various forms of cancers. There are no current studies in humans for obvious reasons, as the result of any such trial would take many, many decades to prove this point!

Caloric Restricted organisms also have a more youth-like appearance (e.g. in rodents or dogs- the colour and texture of the fur) and greater physical mobility and energy levels.

In 1995, Dr. Leonard Guarante and his team at the Massachusetts Institute of Technology identified a longevity gene called Sir2 in yeast. Researchers also noted that the greater the number of Sir2 gene copies in a particular strain of yeast, the longer its life span. Furthermore, caloric restriction-like conditions (e.g. yeast grown in lower glucose concentrations) also stimulated extra copies of Sir2 genes with a subsequent increased life span.

The next step was to see if such a longevity factor was present in mammals. Indeed, a family of genes were identified and categorized as Sirt1. Both these longevity genes, Sir2 in yeast and Sirt1 in mammals, in turn produce a class of protein enzymes called sirtuins, which are thought to exert a myriad of health and life extension benefits. It seems that sirtuins modulate the various biological disease markers as well as numerous cell-signaling pathways. Sirtuins are a particular type of enzymes known as deacetylases, which function to remove acetyl groups (CH3CO-) from a variety of biological compounds and subsequently activating them and exerting life extension effects. Caloric restriction raises sirtuin levels. Inhibition of sirtuins results in opposite effects e.g. decreased life-span. Studies with genetic mice that have had their Sirt1 genes deleted were unable to generate any sirtuins and did not show any extension of life span when caloric restricted conditions were imposed. Researchers believe that some of the beneficial effects of caloric restriction are exerted via sirtuins.

The next question was to see how caloric restriction activated the sirtuins. Imposition of caloric restriction is a stress-like condition for an organism. Evolution has prepared organisms to better adapt to various stresses by shifting the metabolism from fermentation (a more wasteful mechanism but prevalent under conditions of plenty e.g. a typical affluent diet) to respiration. The latter is a more economical and better mechanism for conservation and utilization of glucose, the key energy molecule during times of scarcity (e.g. caloric restriction). The mechanism of how sirtuins work is not completely understood but is believed by some researchers that sirtuins seem to act as fuel sensors, (much like the fuel gauge in a car) monitoring the metabolic state of cells and thus adjusting the life and health span accordingly. Later researchers identified a "Master switch" gene called PNC1, because it regulates the Sirt1 genes and the sirtuin production (see figure 1).

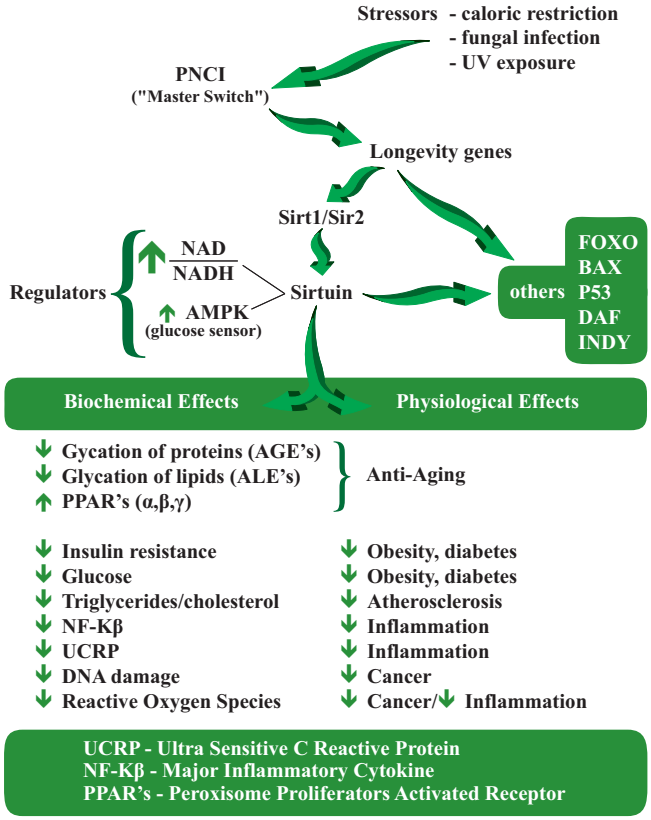

Figure 1. Caloric Restriction/Resveratrol and biochemical/Physiological effects

Researchers wanted to know how sirtuins were activated by caloric restriction. Again, Dr. Guarente and one of his former students proposed that vitamin B3 plays a major role, particularly in the ratio of its oxidized and reduced forms i.e. NAD/NADH. High levels of NADH inhibited the gene while a high level of NAD stimulated it.

Numerous theories have been proposed to explain how caloric restriction works, however none of the theories can completely explain all the life extension and health benefits. These include: reduced rate of metabolism (hence reduced generation of free radicals), lowered levels of various hormones particularly the stress hormones, reduced levels of insulin and insulin-like growth factor, lowered glucose, fat content and reduced protein turnover. Researchers believe that caloric restriction, at its most fundamental level, triggers a kind of global survival mechanism in the body that forces it into a higher overall state of efficiency.

Recently, this has been formalized into what is now known as the Hormesis theory. This is an elegant and novel proposition of the workings of caloric restriction. The survival mechanism may result in the stimulation of longevity genes as in the case of yeast, worms, fruit flies and rodents. In the case of plants, it is the release of compounds that afford protection to the stressed plant. Moreover, these compounds are not only effective but are non-species specific! In other words, phytochemicals produced by the stressed plant may be used by other species to warn them of not only impending changes of scarcity (or environmental changes) but also to stimulate their own defenses. For example, grapes with fungal infections release various polyphenolic compounds (quercetin, fisetin, apigenin and resveratrol to name a few) called phytoalexins. These phytoalexins attenuate the fungal infection via an anti-fungal and/or anti-biotic effect, or by stimulating the survival genes. Phytoalexins may also be effective when used by other species to activate their own defenses.

The Science of CR Mimetics

Despite excellent epidemiological evidence of reduced morbidity and mortality following caloric restriction, the prospect of maintaining a low calorie diet is pretty daunting. Moreover, there is extensive lobbying, promotion and misinformation by multinational food corporations, the fast food industry and big pharma to discard any effects of caloric restriction! In light of these difficulties, researchers have focused their attention on compounds that mimic the effects of calorie restriction by targeting the same biochemical pathways but without restricting the calories. In other words, having your cake and eating it too! Such compounds are called CR Mimetics.

RESVERATROL

Resveratrol is a naturally occurring polyphenolic compound found in various berries (cranberry, blueberry, grapes), peanuts, rhubarb and a number of oriental herbs including the Japanese Giant Knotweed (Polygunum cuspidatum). (See figure 2 for chemical structure).

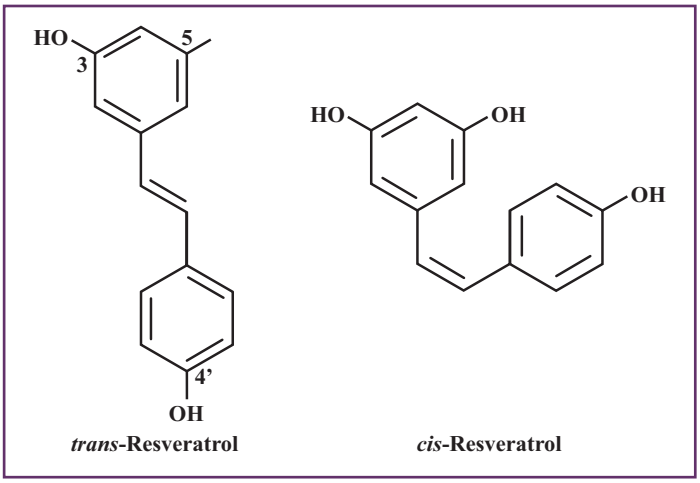

Figure 2. Different isomers of Resveratrol

Studies with resveratrol have reported a diverse range of physiological and biochemical effects particularly in the areas of heart health, cancer, immunity and inflammation. For example, the " French paradox"- the anomaly of high fat consumption and yet a low rate of heart disease in the French population has been attributed to the consumption of wine and the

phytochemicals present in the wine. Other beneficial cardiovascular effects include the reduction of cholesterol and triglycerides, dilation of blood vessels (hence a blood pressure lowering effect), platelets being less "sticky" (anti-aggregatory effect)- and consequently a lower incidence of atheroma or plaque formation and a reduced rate of strokes and heart attacks. Resveratrol exerts anti-oxidant effects by quenching free radicals (including reactive oxygen species). This reduces the oxidation of LDL particles which many believe to be the initiating event in atherosclerosis or hardening of the arteries.

Inflammation has been linked to a whole host of conditions, including osteoarthritis, heart disease, auto-immune diseases (e.g. multiple sclerosis and Crohn's) and cancer. Resveratrol has been shown to down-regulate the production of chemicals (cytokines) involved in the cause, signaling and amplification of inflammation. Resveratrol's anti-cancer effects have been shown to occur at all three stages of cancer - initiation, promotion and progression. Resveratrol prevents the blood flow to tumours which restricts the growth and spread of cancer cells. Resveratrol also inhibits various enzymes involved in cancer formation (e.g. cyclooxygenses or ornithine decarboxylase). Finally, the modulation of the activity of the two groups of enzymes - Phase 1 and Phase 2 - also plays an important role in the detoxification and anti-cancer effects of resveratrol. The Phase 1 family of enzymes normally makes compounds more carcinogenic or toxic and resveratrol has an inhibiting effect on them, thereby preventing carcinogen formation. Alternatively, stimulation of the Phase 2 class of enzymes help facilitate the removal of toxins and carcinogens from the body by making these compounds even more soluble and easier for excretion. Finally, resveratrol also inhibits unfavourable cellular proliferation and up-regulates apoptosis or programmed cell death.

Resveratrol is the phytoalexin compound produced by grapes in response to stressors like fungal infection or ultra violet exposure. David Sinclair and his group at Harvard University have screened numerous plant compounds and found resveratrol to be the most potent. Resveratrol has been shown to enhance life extension much like caloric restriction in yeast (70%), worms (18%), fruit flies (30%), and fish (60%). The mechanism may be similar to sirtuin activation. There is considerable excitement regarding the use of resveratrol as a CR Mimetic. A recent study published in the prestigious journal Nature jointly by Sinclair's group and the National Institute of Aging demonstrated that resveratrol in high doses offsets the effects of an unhealthy high-calorie diet in mice.

In this study there were three groups of mice. The first group was fed a high fat diet, the second group had similar diet but were also given resveratrol, and the third group was fed the standard calorie-restricted diet. As expected the mice in group 1 developed obesity and diabetes with changes in various organs (e.g. enlarged livers) and started to die early compared to the group 3 mice that did not develop diabetes, obesity or organ changes and lived longer. However, the mice in group 2 also became obese due to the high fat diet but did not develop diabetes or enlarged livers. Moreover, these mice lived as long as group 3 mice and longer by 30% over mice in group 1!. As a reporter from the NY Times rather capriciously put it " they (mice in group 2) had all the pleasures of gluttony but paid none of the price!". Furthermore, the resveratrol supplemented mice had better mobility and endurance than group 1 mice.

The study's results are all the more remarkable because all the mice were "middle-aged" (1 year or older) when resveratrol supplementation began. In other words, even when given at this stage of the mice's lives, resveratrol was effective in prolonging life span and improving health. Regarding the various disease markers, the resveratrol treated group had reductions in all levels (e.g. insulin, glucose, insulin resistance and IGF-1) while all the positive markers increased, including AMPK levels and the number of mitochondria. The latter point is interesting as mitochondria are the powerhouse of cells. Another recent study has shown that an increase in the number of mitochondria within a cell is associated with reduction in aging.

Resveratrol and the challenges in formulation

Many resveratrol supplements have recently appeared in the market place. Unfortunately, with resveratrol there are a number of challenges that need to be addressed if one is to achieve any therapeutic efficacy. These are:

1. Stability

Resveratrol is a molecule that occurs in nature in two forms or as mirror-images, namely the trans and cis forms. See figure 2. It is the trans version of resveratrol that has been used in all the investigations. This would appear to be the most active. The cis form may be at best inactive or at worst inhibit the activity of its mirror image - the trans form. There are very few high quality naturally extracted sources that yield 98% plus trans resveratrol activity.

Resveratrol beadlets are stable in oxygen. The issue of oxygen sealed capsules appears to be a marketing ploy by various companies. The main stability issue is centred around light and pH sensitivity. Effective formulations need to offer protection for these obstacles!

2. Dose

There is considerable variation in the doses used in in-vitro (test tubes) and in animal (in-vivo) studies. There is a general consensus that high doses of resveratrol are required to achieve any clinically significant results. The latest animal studies suggest that the comparative human dose needs to be around 300mg (or more) per day for a 70 kg person. Clinical studies currently underway are using even higher doses.

3. Bioavailability

Resveratrol has been shown to be very poorly bioavailable. It readily undergoes metabolism via glucuronidation and sulphation to produce corresponding metabolites. In order to increase resveratrol's bioavailability, one has to inhibit these enzyme systems by using potent and specific substrates for these enzymes. It is possible to achieve this by using quercetin, piperine and luteolin, particularly the latter which has been shown to be the most potent inhibitor of sulphation.

4. Side effects

Researchers have commented on the similarity of the chemical structure of resveratrol with estrogens. While the latest human studies are using very high doses of around 7.5 grams per day with no estrogenic effects, the potential for such effects still exists. Until more studies are published, patients with a familial history of breast, uterine and cervical diseases are best to avoid resveratrol.

As we conclude, we are reminded of the 'one glass of wine a day for longer life' anecdote. In order to obtain the substance identified as responsible for this effect in amounts that are commensurate with even the most conservative trials, one needs to consume approximately 1,000 glasses of red wine each day! A noble goal for some, but perhaps one capsule containing enough resveratrol to equal that found in approximately 450 glasses of red wine might be a more practical start.

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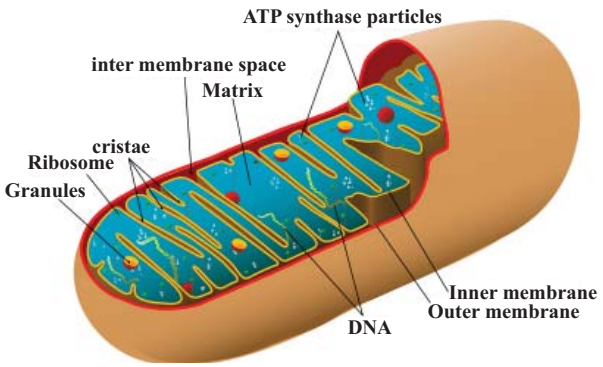
MITOCHONDRIA: MAINTAINING THE POWER PLANT

The Mitochondria. Even the name itself emanates power, centralized activity and importance - and this exudation is not misplaced. The most common metaphors used to describe the mitochondria are the 'powerplants' or the 'furnaces' of the cell. Indeed, mitochondria provide the energy a cell needs to move, divide, replicate, contract, secrete byproducts, and anything else that requires motion and the fuel energy to make it posssible. Mitochondria are bacteria-sized organelles - thousands are located inside the membrane of each cell, occupying about one-fifth of its volume and lying adjacent to its nucleus.[1] Their shape can vary greatly depending on the cell type, and like the nucleus each mitochondrion is surrounded by a double-membrane composed of outer and inner segments. While the outer membrane is relatively smooth, the inner membrane is condensed with folds called cristae, and it is on these cristae that Adenosine Triphosphate (ATP) - the primary fuel of life - is produced. The cristae significantly expand the surface area of each mitochondrion, thereby increasing its cellular respiratory capacity and the ensuing production of ATP. The space within the cristae and the inner membrane is called the matrix, which contains a densely concentrated mixture of several hundred enzymes, ribosomes and DNA precursors. This is indicative of mitochondria's unique level of genetic self-sufficiency, which some scientists argue dates back to a time in evolution when the mitochondria independently sustained themselves outside the cell wall entirely!



The Vicious Cycle

The impressive capacity of the mitochondria to perform their primary function of converting organic materials into cellular energy in the form of ATP cannot be understated. That capacity, however, does not remain constant and is dependent on outside variables, such as diet, lifestyle and age. In fact, it would not be inaccurate to view the state of mitochondria as reflective microcosms of the state of the living organism as a whole.

The Mitochondrial Theory of Aging:

There are several theories of aging, each one identifying and then revolving around one particular biochemical pathway. Examples of pathways these theories depend on include glycation, free radical generation, and methylation, to name a few. Predictably, there is a significant degree of juxtaposition among all of these theories. One theory, however, is the Mitochondrial Decline Theory, or the Mitochondrial Theory of Aging. This theory is closely related to the well-established Free Radical Theory of Aging and has in fact been described by scholars as a 'maturation' of that theory.

This is because the Mitochondrial Theory of Aging begins with the premise that the cellular respiratory process (for which mitochondria are chiefly responsible) results in the production of reactive oxygen species (ROS). This is a vicious catch-22, especially in light of the fact that simultaneously increased mitochondrial activity and proliferation is almost universally associated with health-enhancing metabolic ameliorations. These include (but are no means limited to) an increased basal metabolic rate (BMR) and improved insulin sensitivity, two states themselves identified as panoramic links to the prevention of a myriad of health disorders. However, the greater the simultaneous activity and proliferation of the mitochondria, the more free radicals they generate. Paradoxically, an inefficient mitochondrion generates even more free radicals than an efficient one, since more fuel (in the form of glucose, amino acids and fatty acids) is required for each mitochondrion to produce the same amount of ATP. This results in an increased ratio of ROS-to-ATP production. To complicate matters further, mitochondrial DNA (mtDNA) differs from the DNA of the nucleus and other organelles in that mtDNA has no enzymatic defense against oxidative stressors, self-generated or not.[2] In-vivo studies have provided evidence for the Mitochondrial Theory of Aging so conclusive that one leading researcher summarized it this way: "It is generally accepted that oxidative mitochondrial decay is a major contributor to aging."[3]

Table 1: Non-genetic Strategies to Improve Mitochondrial Dysfunction[4]

Strategy	Theoretical Basis	Example
1. Enzyme Bypass	Provide energy beyond the site of the enzyme defect	Succinate, Co-Enzyme Q10
2. Anti-oxidants	Reduce free radical damage to cell structures	Vitamin E, C, lipoic acid
3. Alternative energy	Use an anaerobic system not requiring mitochondria	Creatine Monohydrate
4. Reduce lactate	Reduce acidosis, more energy into the mitochondria	Dichloroacetate, thiamine
5. Strength exercise	Improve strength, reduce number of mutant mtDNA	Weights, isometrics
6. Endurance exercise	Improve endurance, reduce cardiovascular risks	Jogging, cycling, walking
7. Nucleotide precursors	Prevent depletion of nucleotide pool (for DNA synthesis)	Triacetyluridine
8. Vasodilation	Prevent vascular spasm in MELAS stroke	L-arginine

Power Plant Maintenance - Upgrading With Cocktails

If the function of mitochondria sounds relatively straightforward (at least on a macro-level), then their aforementioned vulnerability reveals a contrasting complexity when the discussion turns to maintenance and enhancement. The process of addressing the elusive prerequisites to mitochondrial health is so intricate that entire professional medical societies have been established exclusively for its study. These include the Mitochondrial Research Society (Buffalo, N.Y.), the Mitochondrial Physiology Network (Innsbruck, Austria), and the United Mitochondrial Disease Foundation (Pittsburgh, PA), among others.

The cumulative efforts of the scientific community have resulted in some measure of fundamental consensus in the design of a protocol to address the challenges posed by an aging and/or dysfunctional mitochondrion. A review of the studies aimed at this goal has produced the following collection of pharmacological, nutritional and exercise treatment strategies - combinations of which have become known as 'mitochondrial cocktails':

1) Enzyme Bypass: The theory here is to circumvent a defect along the mitochondrial Electron Transport Chain, which is a series of inter and intra-cellular reactions that produce ATP. This chain is initiated when electrons are transferred to a lipid-soluble carrier called a ubiquinone, which in turn crosses the cellular membrane. The supplemental form of ubiquinone is Co-Enzyme Q10 (Co-Q10), and studies have shown that it can expedite the Complex II phase of the Electron Transport Chain by up to 200%.[5] This is the phase where additional electrons are funneled into the ubiquinone by the enzyme succinate dehydrogenase.

2) Anti-oxidants: The universal anti-oxidant/free radical dichotomy certainly has mitochondrial applications as well, but the vulnerability of mtDNA alters the circumstances. Conventional anti-oxidants such as vitamins C and E are certainly useful, but the ideal mitochondrial anti-oxidant appears to be a-lipoic acid, or simply lipoic acid (preferably composed of the R(+)-enantiomer - see Advances October 2001 or Vol.3; Issue 1). Lipoic acid is metabolized to its active form, diHydrolipoic acid (DHLA) inside the mitochondrion itself by the enzyme known as pyruvate dehydrogenase complex (PDH). This process, (and equally importantly, the dynamics of this process) produces intense biological activity, including the regeneration and recycling of vitamins C and E.[6] Lipoic acid not only displays an intramitochondrial anti-oxidant capability, but also an intracellular and extracellular one as well, and this capability is effective in both aqueous and lipophilic environments.[7] Indeed, the biological potency of lipoic acid is such that it has become one of the most heavily studied antioxidants in the scientific community, with the result being the development of more advanced variants of this ubiquitous compound.

3) Alternative Energy: This tactic involves the maximal utilization of a source of ATP that does not require any mitochondrial participation, thus augmenting overall ATP production without burdening dysfunctional or aging mitochondria. One way of doing this involves the supplementation of creatine monohydrate for conversion to phosphocreatine (which in turn regenerates ATP) by cytoplasmic creatine kinase enzymes. Studies have in fact confirmed creatine monohydrate's effectiveness as an alternative energy

source of this kind.[8] However, other alternative (and highly promising) sources of ATP originating outside the mitochondria have also been isolated in recent years - not the least of which is exogenous ATP itself. The ATP molecule has been replicated in the laboratory through scientific fermentation, and numerous clinical human studies have already demonstrated its ability to augment ATP pools.[9]

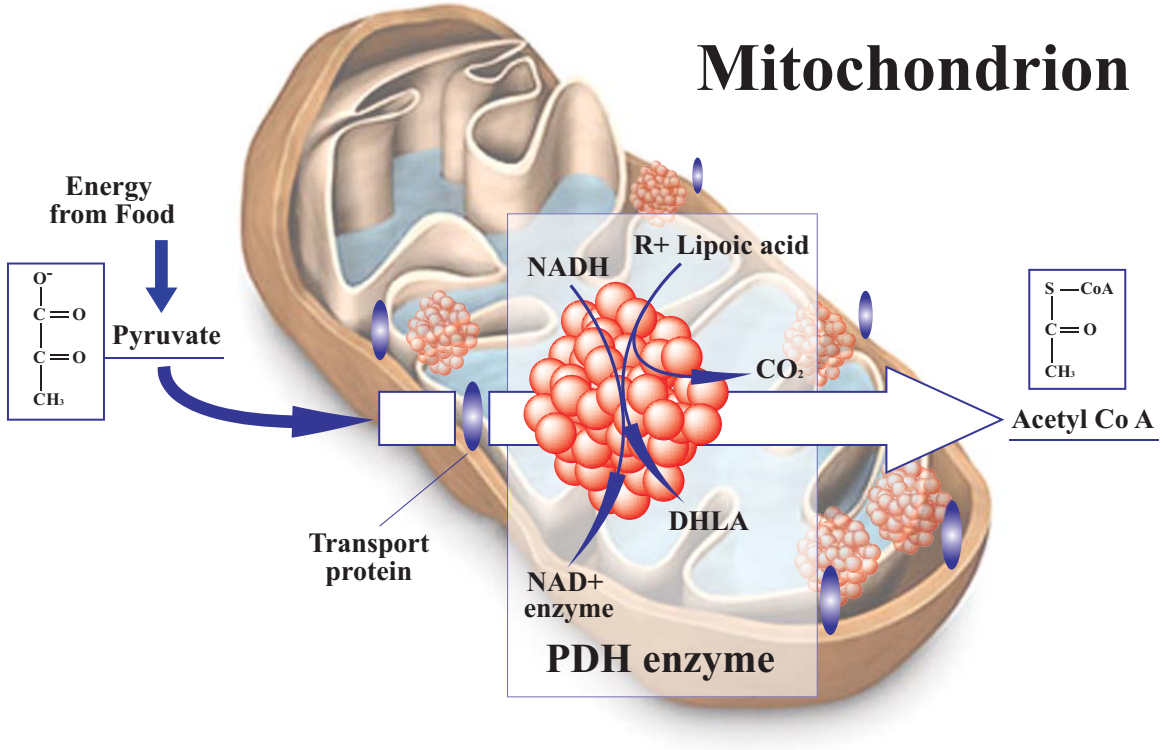
4) Reduce Lactate: Lactic acidosis is the condition whereupon the mitochondria use glucose for energy in the absence of adequate amounts of oxygen, and this cellular hypoxia is linked to mutations in mtDNA.[10] The strategy here is to stimulate the enzyme pyruvate dehydrogenase - which is responsible for directing pyruvate into the mitochondria and away from lactate production. This can be done with the drug dichloroacetate as well as with vitamin B1 supplementation.[11] The latter option has been made even more appealing by the development of benfotiamine, a lipid-soluble thiamin that is nearly 5 times more bio-available than conventional thiamin.[12]

5) Strength Exercise: Studies have shown that resistance training reduces oxidative damage to all DNA as well as 'significantly increasing' the activity of Complex IV of the Electron Transport Chain.[13]

6) Endurance Exercise: Extensive human studies conclusively point to the ability of endurance exercise to improve the activity and efficiency of the mitochondria. For example, one Australian study among obese adults revealed that endurance training increased mitochondrial fatty acid oxidation by 120%.[14]

7) Nucleotide Precursors: Nucleotides are the structural units of DNA and RNA - including mtDNA and mtRNA. As mitochondrial dysfunction is closely associated with the depletion of nucleotides, maintaining a healthy nucleotide pool is paramount. Triacetyluridine, a chemoprotective drug that is a precursor of uridine (an RNA nucleotide), is believed to be capable of this. Naturally-derived uridine supplements have been studied for their ability to improve mitochondrial function in patients with HIV.[15] The supplement D-ribose, itself a structural unit of uridine, has been shown to reduce symptoms of fybromyalgia and chronic fatigue syndrome (both closely identified with mitochodrial dysfunction) by 30%.[16]

8) Vasodilation: Vasodilation (the widening of the blood vessels due to relaxation of smooth muscle in the vessel wall) is linked to the mitochondria via the production of nitric oxide. The mitochondria are primary targets of nitric oxide, and even small amounts can regulate ATP synthesis.[17] MELAS (or mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) is a mitochondrial disorder caused by mutations in the mtDNA of endothelial cells that lead to their dysfunction. As its name implies, lactic acid buildup and stroke-like seizures are among the most common symptoms of MELAS, and supplementation with L-arginine, a nitric oxide donor, has been shown to ameliorate such symptoms in MELAS patients.[18] Other nitric oxide enhancers include citrulline malate and the highly efficient gynostemma pentaphyllum.[19]



NAD+/NADH: All the Difference A Letter Makes

A central facet of mitochondrial health revolves around the NAD+/NADH relationship. This is the process whereupon nicotinamide adenine dinucleotide is converted from its oxidized form (NAD+) to its reduced form, NADH; with the 'H' representing a hydrogen atom. This hydrogen atom is appropriated by the mitochondrial pyruvate dehydrogenase enzyme (PDH) along with the R(+)- enantiomer of lipoic acid to create dihydrolipoic acid (DHLA). An increasing central principle to mitochondrial (and overall) health is the importance of maintaining a favourable ratio of NAD+ to NADH, and there are a number of reasons for this.

Firstly, if there is insufficient R(+)-lipoic acid present to make use of the excess hydrogen atoms, then they are greeted by a mitochondrial PDH enzyme that cannot make use of them. The result is that these atoms eventually become superoxide radicals from inside the mitochondrion itself.[20] Secondly, the reduced form of nicotinamide adenine dinucleotide (NAD+) is the form that is readily available to the mitochondria as an energy source. Thirdly, a low NAD+/NADH ratio has been linked to diabetes, ischemia conditions, and metabolic syndrome, all of which in turn have strong ties to mitochondrial dysfunction.[21]

A metaphor for the NAD+/NADH ratio could be the revolutions per minute (RPM) of a car engine. If vehicle A requires it's engine revving at 6,000 rpm to travel at 100km/hr while vehicle B requires 4,500 rpm for the same speed, then vehicle B is the more efficient machine.

Interventions known to produce a favourable NAD+/NADH ratio include R(+)- lipoic acid, carnosine, 3-carboxy-3-oxopropanoic acid, and the practice known as Calorie Restriction (CR).[22] No 'mitochondrial cocktail' would be complete without something to address this central relationship.

As we have seen, the optimum maintenance of the mitochondria, the powerplant of the cell (and by extension of life itself) requires an approach that is both multifaceted and flexible. The importance of flexibility is due to the fact that research in this area is both extensive and ongoing, and new developments have to be incorporated into an intervention regimen that can already be quite complex. Examples of these new developments include such innovations as the isolation of the active enantiomer of lipoic acid [R(+)-lipoic acid], a Kreb's Cycle intermediate such as 3-carboxy-3-oxopropanoic acid, and a bioactive sirtuin activator such as trans-resveratrol.[23] These form an exciting new class of compounds known as 'calorie restriction mimetics', so named for their ability to emulate many of the health benefits of a calorie-restricted diet, for which the mitochondria are of central importance..

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Q&A

Life Extension; Adding Years to Life and Life to Years

Q What exactly is Life Extension and what do I have to do to achieve it? Will my life have to revolve around gym hours, bizarre diets and endless pill popping?

A The short answer to the second half of that question is NO on all counts, but let's begin with the concept of Life Extension itself.

First and foremost, life extension, while literally meaning to extend one's lifespan, also means to extend one's health span. It is about maintaining the health and vitality associated with youth for as long into one's life as possible. Of course, maintaining such an optimal level of health can lead to longer life, but more on that later.

Diet, exercise, and supplementation will have to become integrated into your life, that much is true. However, the accumulated disruptive effect of these factors does not have to be as extensive as you may think. To date, the only CLINICALLY PROVEN method to extend lifespan in mammals is Calorie Restriction (CR), or Calorie Restriction with Optimum Nutrition (CRON). The latter term says it all in five concise words. Simply eat less food calories than your body thinks it needs, while maintaining optimum levels of essential nutrients. This means selecting food that has the highest nutrients and the fewest calories. If yours is a typical North American diet, you would probably have to eat significantly more fruits and vegetables and significantly fewer cereals and grains. You will also have to cut out sugar, refined carbohydrates and saturated fats as completely as possible. Figure 1 provides a food pyramid of what a typical CRON diet would look like. This is not some bizarre, fad diet. It is a lifestyle choice, and if implemented gradually, on a step-by-step basis (i.e. on the first month drop sugar, the next month drop saturated fat, etc.) it can be a relatively painless choice at that.

As far as exercise is concerned, more is not necessarily better. The types of exercises advocated by life extensionists are actually as modest as they are varied, and they can be seamlessly integrated into most people's lives. One Harvard study found that 30 minutes a day of simple walking at an average pace for 5 days a week cut the risk of stroke by 24%.[1] The same benefits can be obtained from playing with your children or simple exercise after work - nothing extreme here either. Furthermore, such physical activity has been shown to accentuate the effects of a CRON diet.[2]

As far as supplementation is concerned, antioxidants are a must, as free radical generation has been shown to increase with age.[3] Vitamin C, full-spectrum vitamin E, and R(+)-Lipoic acid are optimal nutrients to add to a complete and balanced multivitamin/multimineral formulation to address this one avenue of aging.

Another avenue of aging is the development of advanced glycation endproducts, appropriately known as AGE. This is the process whereupon sugars in your body such as fructose or glucose bind to bodily proteins or lipid molecules without the mediating action of an enzyme, leading to the formation of AGE, which in turn can eventually lead to stiffening and loss of function. AGE are common among diabetics, which is why diabetes has been referred to as a form of 'advanced aging'. Benfotiamine and pyridoxamine, two unique and highly advanced forms of vitamins B1 and B6 which have been shown in clinical studies to inhibit AGE and thus addresses another major front in the battle against aging.

A third fundamental avenue of aging is methylation, a metabolic process so pervasive that it affects everything in your body from nerve transmission to gene expression. However, the methylation process also produces a toxic by-product known as homocysteine. Elevated levels of homocysteine can cause particular damage to cells lining the arterial walls, potentially leading to premature arterial deterioration and/or early heart disease. An efficient methylation (or more accurately, a 're-methylation) system will safely recycle much of the homocysteine it produces, but this is highly dependent on adequate nutrition. Additionally, homocysteine levels have been shown to rise with age.[4] An exceptionally effective substance known to inhibit homocysteine is trimethylglycine (TMG), also known as betaine.[5]

Finally, there is an exciting new substance that mimics the effects of the CRON diet itself, and this substance is called 3-carboxy-3-oxopropanoic acid.

Designing a supplement regimen that is based on accentuating the CRON diet as well as addressing the three previously identified main avenues of aging thus far, namely free radical production, AGE, and methylation, certainly does not have to be excessively complicated - particularly in light of the examples given.

Q Is there any proof that all this actually works in the real world, not just in the lab? If so, how?

A An excellent question. The body of evidence supporting the CRON diet is overwhelming. For the sake of brevity, we will not delve into the hundreds of studies among laboratory animals (including primates - who share as much as 98.3% of our DNA) whose lifespans were extended using CRON.

If we look at human studies, the evidence supporting the CRON diet is extremely encouraging. You will notice that the word evidence is used as opposed to outright proof, but there is a perfectly valid reason for this. Determining if CRON could actually extend the lifespans of adult humans would take the better part of a century and cost prohibitive amounts of money, not to mention the fact that the scientists running the experiment would all be dead before the final results could be determined. However, a chronological anomaly in human existence has provided us with a very approximate snapshot of what a human population may look like under the CRON diet: Okinawa.

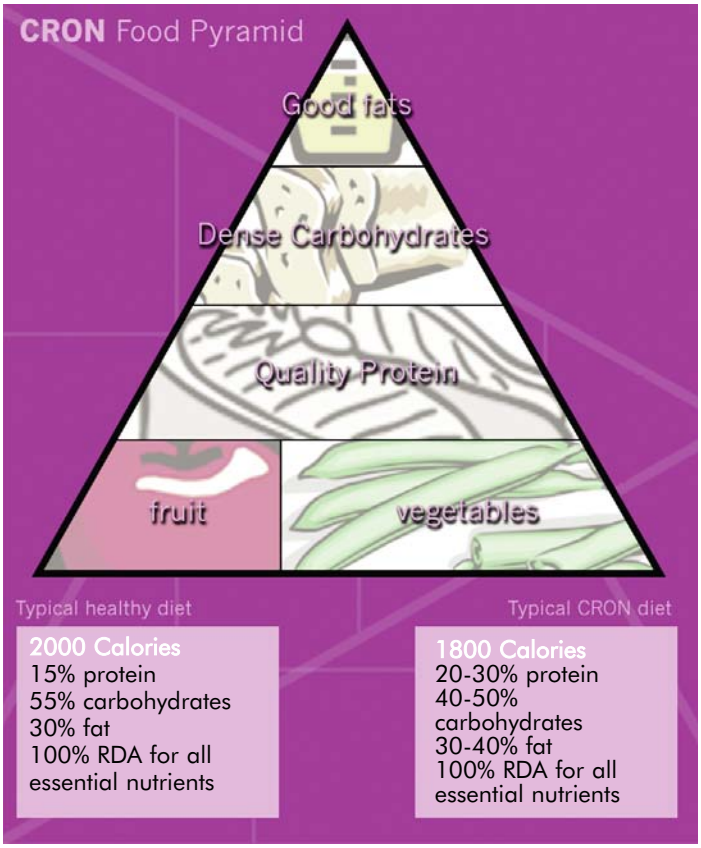

Figure 1. CRON Food Pyramid

The 1.3 million citizens of the Japanese island of Okinawa have always led an isolated existence from their mainland compatriots, leading to the development of a distinct dialect, culture...and diet. This isolation was extended with the US military administration of the island that lasted until 1972. The pre-1972 diet of Okinawans depended heavily on local vegetables, with protein limited to poultry and fish (the latter also serving as the primary source of essential fats). Most importantly, the Okinawan diet contained one-sixth fewer calories than that of mainland Japan, mainly due to a lower intake of grains and sugars. In short, the traditional Okinawan diet is very much in line with a conservative CRON diet.[6] The result is that the island of Okinawa has by far and away the highest percentage of centenarians (people aged 100 years or more) of any geographic entity on the planet. A study in 1990 showed mainland Japan averaging 21.6 centenarians per 100,000 people, a figure considered to be the highest in the developed world; the US averaged 15.0 - and Okinawa averaged an astonishing 133.8![7] Furthermore, unlike the now-disproven longevity myths of isolated communities in the Caucasus and Latin America, the aforementioned figures can be verified by astute Japanese census bureau data.

Returning to the lab, human scientific studies of practical durations (weeks and months) have revealed that people on a CRON diet can expect better blood sugar,[8] insulin,[9] cholesterol,[10] and blood sugar levels.[11] The connection between these improvements and the effects they can have on life extension are simply undeniable.

One human trial revealed that the CRON diet may prevent colon cancer,[12] while another found that it can lower the risk of breast cancer in women,[13] and yet another revealed an underlying force that may just possibly explain the effects of the CRON diet in a nutshell. This particular study demonstrated that the CRON diet induces key hormonal metabolic changes, forcing the body to take steps to use energy more efficiently and thus utilize nutrients more effectively.[14]

Returning to the area of supplementation for a moment, 3-carboxy-3-oxopropanoic acid is designed to influence many of the same genes affected by the hormonal metabolic changes induced by the CRON diet. In fact, in a soon-to-be published study conducted with laboratory mice, it was found that 356 different genes were affected in the same way by 3-carboxy-3-oxopropanoic acid as they were by the practice of calorie restriction. Studies with this exciting new compound are ongoing.

The supplemental protocols to counter the three known avenues of aging can also claim exciting study results to their credit. A 2007 study confirmed that there are declines in plasma concentrations of antioxidants such as Vitamin C that are age-dependent,[15] reaffirming the need for antioxidant supplementation in the golden years. As far as AGE (advanced glycation endproducts) are concerned, benfotiamine can boast numerous human studies, particularly with those suffering from diabetic neuropathy, which is the deterioration of the nervous system due to diabetes, with AGE playing a significant role in that deterioration. We have already discussed how diabetes can be referred to as a form of 'advanced aging'. Benfotiamine was shown to improve nerve function in diabetic nephropathy sufferers by as much as 30% in one human study,[16] while alleviating diabetic nerve pain by 50% in another.[17] This was achieved through benfotiamine's inhibition of AGE, and AGE occurs in everyone to varying degrees and has been shown to be clearly associated the aging process.[18]

We have already mentioned the importance of methylation, and how the trimethylglycine (TMG)-led protocol can inhibit the homocysteine that methylation produces. In fact, studies have demonstrated that TMG can lower homocysteine levels by as much as 30%, making TMG the most effective homocysteine-lowering substance known.[19]

Finally, we have also mentioned how physical exercise can amplify the effects of the CRON diet and prevent the onset of certain disorders. Yet there are further clinical trials that prove that even modest exercise regimens such as assisted walking can improve mobility and independence among the infirmed elderly.[20] From this example, it is not difficult to envision the preventative benefits of lifelong physical activity, and nothing can encapsulate the message of 'adding life to your years and years to your life' more clearly than that.

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