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## **Longevity and Epigenetic Modification (Intermediate Level NH)**

### **Intro**

Human longevity is influenced by multiple genetic, epigenetic and environmental factors. The genetic component is estimated at 25-32%, however it has long been known not only that key genes are involved in the aging process but that some of these can be strongly affected by epigenetic factors. Instead of being the result of an accumulation of genetic and cellular damage, new evidence suggests that aging occurs when genetic programs for development go awry.

Mainstream healthcare information sites have begun bleating about lifestyle and mental health as society struggles to support a growing number of aging dependants in the healthcare system and it doesn't take much forethought to see that this is an escalating problem.

As Neurohackers it's our aim to enjoy a long life free from mental problems as we age, and looking at epigenetic factors and how they work can give us pointers for healthy adjustment. We're already aware of how to hack one key gene related to aging via a low GI diet, and this article looks at what other steps may be possible to prolong good mental health using input control to affect epigenetic changes.

We continue to update research progress and you will find the most recent information towards the end.

### **2000BCE: Astragalus Mongholicus**

The Chinese discovered that the root of the herb "Huang Qi" (aka *Astragalus mongholicus*, *Astragalus membranaceus*, *Astragali*, *Beg Kei*, *Bei Qi*, *Buck Qi*, *Hwanggi*, *Membranous Milk Vetch*, *Milk Vetch*, *Mongolian Milk*, *Ogi*, *Astragalus*) "generates flesh" and speeds healing, as well as being a vasodilator. They didn't know about telomeres in those days (see 2008 article

below) but used the root for age-related problems.

### **2000: 25:75**

Results from major twin studies indicate that approximately 25% of the variation in human life span is genetically determined. This means that 75% of it isn't!

### **2001: The Human Genome Project Had a Working Base**

Approximately 55 genes had been identified that could extend longevity when altered. These include an insulin-like receptor (*daf-2*) and a phosphatidylinositol 3-OH kinase (*age-1*) regulating a forkhead transcription factor (*daf-16*), as well as genes mediating metabolic throughput, sensory perception, and reproduction.

Some of these alleles both extend life span and increase resistance to ultraviolet (UV) radiation, heat, and oxidative stress. Studies revealed a new system for specifying longevity and stress resistance and suggested possible mechanisms for mediating life extension by dietary restriction and hormesis.

### **2001: Free Radical Damage**

The idea that heat stress and reactive forms of oxygen—"free radicals" that are the normal by-products of metabolism—cause aging has been around for 50 years. Studies have shown that reducing exposure to reactive oxygen species increases life span, and animals that have been bred to live longer are also more resistant to heat stress. But few studies had definitively linked oxidative damage to altered cellular function.

### **2001: CETP Inhibition and Coronary Heart Disease**

Several genetic variants at CETP locus have been identified and they have been generally associated with increased HDL-cholesterol concentrations.

Most research on CETP has looked at the CETP gene and its variants in the context of HDL and impact on cardiovascular disease processes, and it was originally thought that these gene variations could be life-extending because the higher HDL would be cardioprotective.

### **2003: Cholesterol & CETP**

Cholesterol processing drew attention in longevity research when it was found that a higher density of lipoprotein (HDL) also referred to as good cholesterol, was present for centenarians.

Cholesteryl ester transfer protein (CETP), also called plasma lipid transfer protein, is a plasma protein that facilitates the transport of cholesterol esters and triglycerides.

Mutations leading to increased function of CETP have been linked to accelerated atherosclerosis.

In contrast, a polymorphism (I405V) of the CETP gene leading to lower serum levels has also been linked to exceptional longevity. High levels of low-density lipoprotein (LDL) cholesterol and low levels of HDL cholesterol are correlated with increased incidence of cardiovascular disease. Individuals with exceptional longevity have significantly larger HDL and LDL particle sizes, associated with a lower prevalence of hypertension, cardiovascular disease (CVD) and metabolic syndrome. Small LDL particles penetrate more readily into arterial tissue, bind more tightly to arterial proteoglycans, are oxidized more rapidly than larger LDL particles, and are associated with endothelial dysfunction, all mechanisms involved in the development of CVD. These findings suggest that (a) lipoprotein particle sizes are variable and (b) larger particles promote healthy aging.

### **2004: Inflammation**

Ageing is found to be associated with chronic, low grade inflammatory activity leading to long term tissue damage, and systemic chronic inflammation is related to mortality risk from all causes in older persons.

The genetic constitution of the organism interacting with systemic inflammation may cause defined organ specific illnesses.

Diseases such as Alzheimer's, Parkinson's disease, atherosclerosis, type 2 diabetes, sarcopenia, and osteoporosis are initiated or worsened by systemic inflammation, suggesting the critical importance of unregulated systemic inflammation in the shortening of survival in humans.

Proinflammatory cytokines are believed to play a pathogenetic role in age related diseases, genetic variations located within their promoter regions have been shown to influence the susceptibility to age related diseases, by increasing gene transcription and therefore cytokine production.

### **2005: SIRT1**

Scientists have known for several years that an extra copy of the SIR2 gene (SIRT1 is the human equivalent) can promote longevity in yeast, worms and fruit flies. But having 2 x SIRT1 seems to have a similar life-extending effect to a peculiar hack that includes its deletion!

Deleting the gene altogether and using caloric restriction and/or a mutation in one or two genes that control the storage of nutrients and resistance to cell damage (RAS2 and SCH9), resulted in a dramatically extended life span; up to six times longer than normal - one of the longest recorded life-span extensions in any organism. Human cells with reduced SIRT1 activity also appear to confirm that SIRT1 has a pro-aging effect.

These findings do not negate discoveries of a moderate increase in life span when SIRT1 is over-expressed.; it just shows that there are possibly greater potential benefits in tweaking it in the opposite direction.

It's possible that SIRT1, in response to transcriptional signaling frequency or type may block the organism from entering an extreme "growth & repair" survival mode (characterized by absence of reproduction, improved DNA repair, increased sleep, less motion, and increased protection against cell damage). Organisms usually enter this mode in response to extreme heat/cold or starvation and show extraordinary resilience under stress. Biology, if it thought consciously, would be thinking, "There are not enough resources to thrive. I will cut all non-essential systems in favor of self care until conditions improve."&quot;

Low GI dieting may activate aspects of this response mode, such as stress resistance, even when food is plentiful. With optimal nutrition, all organisms have the ability to repair harmful mutations in their DNA, whether caused by age, radiation, diet or other environmental factors. (Cancer often begins when DNA mutations outstrip a cell's ability to remain differentiated.)

### **2005: HDL**

A number studies have supported a possible life-extending role for CETP variants in the contexts of lipids, raising HDL, and preventing cardiovascular diseases. Other beneficial biological properties of HDL have been described, including anti-inflammatory, antioxidant, antiaggregatory, anticoagulant, and profibrinolytic factors. There is increasing evidence that factors that protect the cardiovascular system also protect against dementia, but the findings are not yet conclusive.

### **2006: Targets for Epigenetic Modification**

There are several key genes whose behavior is now known to be associated with aging. They mainly affect four processes in biology which are: Insulin/glucose processing, Cholesterol processing, Inflammation and Telomere length.

### 2006: CETP and Dementia

Studies found that those who inherit a particular genetic variation of the gene CETP ((I405V); previously linked to longevity) are twice as likely to have a sharp and alert brain when they are elderly. They are also five times less likely than people with a different version of CETP to develop Alzheimer's disease and other forms of dementia.

The favorable gene variant alters CETP so that the protein functions less well than usual. People with the protective variant produce a less active version of CETP protein. The variant affects cholesterol metabolism, boosting levels of high density lipoprotein (HDL), also known as "good" cholesterol. HDL plays an important role in the membranes of nerve cells in the brain.

Those with two copies of the protective variant had a 70 percent lower chance of developing Alzheimer's and other dementias, as well as a significantly lower rate of memory decline. This may in part be due to improved blood flow. They were twice as likely to pass tests of mental agility, had better cognitive function, and were five times more likely to be protected from dementia and perform well in memory tests.

The findings support the link between cholesterol levels and dementia.

Previous research on mice that were engineered to mimic Alzheimer's found that CETP inhibitors provided modest protection against the disease.

CETP has two functions: it helps move cholesterol from the arteries to the liver, and it helps control the size of cholesterol particles circulating in the blood. People with the protective gene variant have increased blood levels of high-density lipoprotein (HDL) - the so-called good cholesterol - but also larger-than-average HDL and low-density lipoprotein (LDL) particles, which may not stick to blood-vessel walls as easily as small particles do.

It's not yet clear exactly how CETP affects the brain, but Cholesterol is an important component

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of brain cells, and cholesterol levels in the blood also affect the health of blood vessels that supply the brain with oxygen.

So, variants in the CETP gene appear to be protective against cardiovascular diseases and also protective against memory decline and dementia.

The frequency of the protective CETP variant in the general population is not well known. Studies have found that about 5% of 60-year-olds have it, about 8% of people aged 70 and approximately 25% of centenarians. The main research from NH perspectives is to find epigenetic factors that affect CETP in similar ways, and the low-GI diet seems to be one way in by manipulation of lipids. Resveratrol may be another, but evidence for why is still lacking (2010).

### **2007: Calorie Restriction, Insulin / Glucose Processing & 'FOX' Genes**

It has been known for over 70 years that a calorie-restricted (CR) diet can increase life span. The biological mechanism underlying this effect is a transcriptional factor (or gene/substance that controls the regulation of other genes in the genome).

Thus far, longevity research involving CR has focused on an insulin-signaling pathway, assuming the levels of nutrient-sensing hormone fall in response to lowered food intake, activating a DNA-binding protein (daf-16) that would then work with a co-regulator in the pathway called SMK-1 to confer longevity through the regulation of genes under its control.

The latest gene found to be involved in longevity via CR is called Pha-4. It seems to affect the same targets as daf-16, and interestingly researchers have found highly increased life spans in animals whose production of daf-16 has been blocked.

Another gene, SIRT1, has also been linked to this kind of longevity, although its effects seem to influence several different pathways whereas pha-4 is the first discovered direct transcriptional regulator of dietary restriction. (PHA-4 is specific for calorie restriction as it does not affect the

other pathways.)

pha-4 has three mammalian homologues (similar genes serving similar functions) falling under the FOXA family of genes, which regulates the pancreatic hormone glucagon in the pancreas and liver. Glucagon counters the ill effects of fasting by modulating blood sugar and controlling energy balance.

The FOX gene family provides instructions for making proteins that play a critical role in the formation of many organs and tissues before birth. These proteins are transcription factors (they help control the activity of many other genes), and they are involved in many aspects of embryonic development. FOX proteins regulate gene activities in the eyes, lungs, brain, cardiovascular system, digestion system, immune system, and cell division cycle. The FOX genes are named with a letter and a number in order to identify which FOX gene subfamily they belong to. Members of the class FOXO regulate metabolism, cellular proliferation, stress tolerance and probably lifespan.

A variation in the gene FOXO3A has a positive effect on the life expectancy of humans, and is found much more often in people living to 100 and beyond – what's more, this appears to be true worldwide. The FOXO3A gene is an evolutionarily conserved key regulator of the insulin-IGF1 signaling pathway. This “master regulator” affects diverse biological pathways including stress resistance, apoptosis, immunoregulation and inflammation.

There's now conclusive evidence that polymorphisms in this gene are indeed associated with the ability to attain exceptional old age. Those lucky dudes with two copies of FOXO3A gene are likely to live longer, healthier lives than those without them, but only if the genes are healthily expressed. All of us have at least one copy, but carrying around copies of longevity genes that have been turned OFF will not help your lifespan at all, so it's important to understand how epigenetic factors affect these genes.

FOXO3A is associated with insulin-regulating proteins and helps with maintaining a balanced metabolism.

Insulin is a hormone that is mainly responsible for the way that we process food and convert it into energy. To cut a long story short, it seems that much of the success of CR and low GI is

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due to reduced insulin levels and enhanced sensitivity to insulin. Longevity-related physiological changes are reflected in altered gene expression in the pancreas and in different insulin/IGF-1 target organs (e.g. muscle, liver, heart), that result in a slowing of the aging process and increases in the efficiency of mechanisms important to long term survival, e.g. stress resistance. It is certain that insulin receptors are fundamental for longevity.

The potential benefit of Calorie Restriction (60% of 'normal' while maintaining a healthy diet rich in vitamins, minerals, and other nutrients) is obvious as a strategy that consistently prolongs life and reduces the risk of cancer, diabetes, and cardiovascular disease, while staving off age-related neurodegeneration. So it's great that some people are already imposing this strict regimen upon themselves, but what is most surprising is the lack of awareness (even among researchers) that a low GI diet achieves exactly the same aim.

### **2008: Resveratrol**

Claims said resveratrol increases life span in some organisms, by mimicking the effects of caloric restriction.

Studies showed that resveratrol opposed the alteration of 144 out of 153 gene pathways changed by a high-fat diet. Insulin and glucose levels on the high-fat+resveratrol diet were close to those on standard diet. Quality of health was improved, but lifespan itself was not significantly altered.

Topically it shows promise as an anti-cancer agent.

Resveratrol apparently activates the Sirtuin 1 protein that in humans is encoded by the SIRT1 gene. Sirtuin 1 deacetylates proteins that contribute to cellular regulation, moderating response to stressors and promoting longevity). In many species they are known to regulate epigenetic gene silencing and suppress recombination of rDNA.

researchers reported that dietary supplementation with resveratrol significantly reduced plaque formation in animal brains, a component of Alzheimer's and other Neurodegenerative diseases. In mice, oral resveratrol produced large reductions in brain plaque in the hypothalamus (-90%), striatum (-89%), and medial cortex (-48%) sections of the brain. In humans it is theorized that

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oral doses of resveratrol may reduce beta amyloid plaque associated with aging changes in the brain. Researchers theorize that one mechanism for plaque eradication is the ability of resveratrol to chelate (bind) copper.

Resveratrol interacts with biochemistry in extremely complex ways and lack of sufficient research and clinical trials are currently holding back developments (2008).

Resveratrol is found in red wine, but the problem lies in getting sufficient amounts of resveratrol without getting too much alcohol. Resveratrol-containing foods and supplements are an additional option; plums, grapes, blueberries, cranberries, and other plants. T

The most efficient way of administering resveratrol in humans appears to be by direct absorption through the inside of the mouth. Resveratrol given as a drug (SRT-501) 3 or 5g, developed by Sirtris Pharmaceuticals, reaches 5–8 times higher blood levels. These levels do approach the concentration necessary to exert the effects discussed.

Resveratrol is estrogenic and may interfere with oral contraceptives and affect pregnancy or intended pregnancy. This is not yet proven, nor are the long-term effects of high doses.

### **2008: GATA Transcription Factors**

Continued research suggests that genetic programs do drive aging. Genes that function as transcription factors are molecular switches that turn other genes on and off. Of the hundreds of things that can go awry in aging, all seem to trace back to common patterns of transcriptional control: GATA transcription factors; in particular ELT-3, ELT-5 and ELT-6.

GATA transcription factors have been known for their importance in many gene regulations in diverse physiological processes. GATA2 suppresses adipogenesis (the formation of fat-storing cells). Specific roles of GATA factors in immunity also play functionally important roles in pathogen resistance.

The GATA transcription factors ELT-5 and ELT-6 act to downregulate the expression of ELT-3 (ELT-3 activity appears necessary for both stress responses and the lifespan-prolonging effects of dietary restriction). It is also known that ELT-3 is modulated by insulin/IGF-I-like signaling, which controls how an organism's metabolism changes in response to famine. One of the things the insulin-like signaling pathway does during caloric restriction or low-GI dieting is to reset the ELT transcription factors in many organisms "to a younger state."

Many (but certainly not all) genes found to change expression during aging are controlled by ELT-3.

RNA interference (RNAi) against ELT-5 or ELT-6 increases longevity in an ELT-3-dependent manner, so it seems that the protective effects of ELT-3 are reduced or removed entirely when ELT 5 & ELT 6 remain turned on.

These and other discoveries indicate that one or more GATA transcription factors may control a common transcriptional network involved in old age and response to insulin-like signaling. Lifespan regulation by insulin-like metabolic control is analogous to mammalian longevity enhancement induced by caloric restriction, confirming the known link between metabolism and longevity. Research suggests that ELT-3 decreases because ELT-5 and ELT-6 increase, suggesting that age regulation of ELT-3 is caused by drift of an intrinsic developmental program that becomes imbalanced.

### **2009: ApoE3 (Apolipoprotein E) and ApoE4**

ApoE3 is a cholesterol transporting gene unique to humans, that also regulates inflammation and many aspects of aging in the brain and arteries.

However, ApoE4 when expressed in humans can impair neuronal development, as well as shorten human lifespan and increase the risk of heart disease and Alzheimer disease. ApoE4 carriers have higher totals of blood cholesterol, more oxidized blood lipids and early onset of coronary heart disease and Alzheimer's disease.

Given that the LDL lipid peroxidation is triggered by the glycation of ApoE, then the low-GI diet may be protective for those carrying ApoE4.

### **2009: Telomeres & Telomerase**

Researchers have found that telomere maintenance plays a very important role in maintaining the longevity of centenarians, and that there are advantageous variants of genes involved in telomere maintenance.

Those who have lived to a very old age may have inherited mutant genes that make their telomerase-making system extra active and able to maintain telomere length more effectively. For the most part, these people are spared age-related diseases such as cardiovascular disease and diabetes, which cause most deaths, regardless of their lifestyle.

Telomerase enzyme can repair telomeres by adding nucleotide sequences and thereby preventing them from shrinking. There is a clear link between living to 100 and inheriting a hyperactive version of an enzyme (the product of two mutant genes; hTERT and hTERC) that prevents cells from ageing. Many centenarians have this mutant gene, and have higher levels of telomerase which protects the DNA.

Ordinarily, prolonging cell life and making cells divide more increases the risk of damaging mutations that can lead to cancer. But this doesn't seem to be the case in this example so it's likely that other factors are at work in biochemistry.

### **2009: Low GI**

Low GI diets finally hit mainstream news under various titles and formats; the 'Paleolithic diet', the Zone diet and a plethora of similars under different names. They are not popular despite great results -people's main objections being that there is too much hassle preparing unprocessed food or growing your own and that they simply can't get decent fresh food wherever they live. We think these are excuses anxiety unconsciously thinks up so that it won't

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have to give up its corn snacks, but there you go.

Low GI diets appear to achieve better results than calorie restriction for longevity and avoidance of disease.

### **2009: TA-65.1**

Geron Corporation and TA Sciences tell us about their new wonderdrug, TA-65

Unfortunately the only information about this drug currently is from the manufacturers or persons in their employ, but it sounds promising because it's based on a herbal source long known for its healing properties (see 200BCE, above)

Telomeres are a part of your DNA. They are the caps on the ends of each chromosome that ensure your DNA isn't damaged during cell division. Every time your cells divide, your DNA loses a little bit of the telomere. At some point, telomeres get too short and can no longer support cell division. The result of this can be the various conditions associated with old age.

The enzyme telomerase supports cell division. Telomerase enables the cell to divide indefinitely by adding back the bit of telomere lost during each cell division. The problem most of us have is that the telomerase enzyme is turned off, and therefore not helping to secure the telomeres on our DNA strands.

Geron claim that their new drug TA-65 "turns on" the gene that makes telomerase.

It's certainly true that many drugs & chemicals can turn genes on or off, slow them down or stimulate them. And it's certainly true that induced variation can affect the genes that lengthen your life and can turn off genes that lead to chronic diseases associated with ageing.

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Their website tells us, "TA-65 affects genes related to aging and cell division. TA-65 turns on the hTERT gene\* which activates the enzyme telomerase which can lengthen your telomeres."

It's likely though that they are telling the truth about telomerase. Human telomerase activity can be reconstituted in vitro by the essential RNA subunit, hTERC, and the catalytic protein component coded for by the hTERT gene. Both the human telomerase reverse transcriptase gene (hTERT) and the telomerase RNA gene (hTERC) are controlled at least in part at the transcriptional level, so they could be hacked chemically without much trouble.

Then the surprising news:

"TA-65 is a naturally occurring single molecule found in the ancient Chinese herb Astragalus. T.A. Sciences has developed a proprietary process to refine and purify TA-65. Our process begins with tons of plant material harvested from selected farms in one small region in China. In our plant extraction facility, the raw Astragalus root is chopped up and refined. After initial extraction, the base ingredient is further purified and then sent to an outside government testing facility where it is tested for purity, heavy metals, and pesticides. The product is then sent to a FDA certified, start-of-the-art, laboratory for final purification that ends up with 90+% pure TA-65. "

The herb Astragalus is a bit of a 'super-herb'. First of all it's an adaptogen, meaning it helps protect the body against various stresses, including physical, mental, or emotional stress. Astragalus prevents colds and upper respiratory infections, lowers blood pressure, and is used to treat diabetes and to protect the liver.

Astragalus has antibacterial and anti-inflammatory properties. It is sometimes used topically for wounds. In addition, studies have shown that astragalus has antiviral properties and stimulates, protects and supports the immune system.

It has anti-cancer properties and is used for a host of problems; among them to increase the production of blood cells and speed healing. It is used orally for chronic nephritis and diabetes; as a tonic; vasodilator, or hypotensive agent.

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Researchers have already investigated astragalus as a possible treatment for people whose immune systems have been compromised by chemotherapy or radiation. Astragalus supplements have been shown to speed recovery and extend life expectancy (although current 'supplements' do not contain enough of the herb to be effective.)

Recent research indicates that astragalus may offer antioxidant benefits to people with severe forms of heart disease, relieving symptoms and improving heart function. At low-to-moderate doses, astragalus has few side effects, although it does interact with a number of other herbs and prescription medications. Astragalus may also have mild diuretic (rids the body of excess fluid) activity.

You can't actually buy TA-65 without paying for a year's worth of 'therapy', so start planting astragalus and learning how to dry herbs if you want your own for free.

Recommended dosage:

Doses from 1 - 25 g per day are sometimes used. Higher doses may suppress the immune system. For best results, it is recommended to use a standardized astragalus supplement. Recommended doses are as follows:

- Standardized extract: 250 - 500 mg, three to four times a day standardized to 0.4% 4-hydroxy-3-methoxy isoflavone 7-sug.
- Decoction (strong boiled tea): 3 - 6 g of dried root per 12 oz water, three times per day
- Fluid extract (1:1) in 25% ethanol: 2 - 4 mL, three times a day
- Powdered root: 500 - 1,000 mg, three or four times per day

**! WARNING !** Do not use if you are on drugs that suppress the immune system -- Astragalus may counteract the immune-suppressing effects of cyclophosphamide, a medication used to

reduce the chances of rejection in transplant recipients, as well as corticosteroids.

### **2010: A Link Between Cellular Stressors and Immune Responses**

Studies reveal that two GATA transcription factors previously implicated in infection-induced transcriptional responses, elt-2 and ELT-3, are also essential for coordinated tissue-specific activation of osmosensitive gene expression and promote survival under osmotically stressful conditions. In other words, transcriptional responses to osmotic stress mimic responses to bacterial and fungal infection.

The mechanism(s) by which this occurs is currently (2010) unclear but may relate to infection-induced disruptions in osmotic homeostasis. GATA factors may function as key integrators of cellular stressors and immune responses.

### **2010: TERC, GHS & Telomeres**

**Scientists identified definitive variants associated with biological ageing in humans, all located near a gene called TERC.**

Telomeres are parts of chromosomes. We are born with telomeres of certain length and in many cells telomeres shorten as the cells divide and age. Telomere length is therefore considered a marker of biological ageing. Age-associated diseases are more closely related to your biological rather than chronological age.

Chronological ageing (as measured by 'birthdays') tells you how old you are in years, but 'biological ageing' is about wear and tear whereby the cells of some individuals are older (or younger) than suggested by their chronological age.

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The TERC gene is already known to play an important role in maintaining telomere length. What this study suggests is that some people are running a genetic program that causes ageing at a faster rate. As neurohackers, looking for epigenetic factors that alter which genes are expressed should be a priority. Many of us are going to want to “change the script” and reprogram this aspect of the genome. The good news is that so often it is the simple things such as sleep and nutrition that can be so effective. Look into Resveratrol or Astragalus for interesting 'telomere-protectors'.

Telomeres are protected in reproductive cells by the enzyme telomerase. Somatic cells (all cells other than your reproductive cells) do not produce telomerase, however, they do contain the gene for telomerase production. The gene is simply turned off, which causes the telomere shortening process to proceed.

The strategy for longevity is to find out how to turn the telomerase gene back on in somatic cells. Researchers have discovered several chemical compounds that will bind to the repressor protein, which will allow the gene to turn back on. There are studies in progress showing that increasing glutathione levels could provide similar results. Glutathione (GHS) is not a compound you can ingest directly. It is manufactured inside your cells from its precursor amino acids, glycine, glutamate and cystine. You can increase your glutathione levels through dietary manipulation alone. Make sure your diet includes foods rich in the sulfur amino acids your cells need to synthesize glutathione. Whey protein is the easiest and most convenient way to do this, but remember that there are vast differences between whey products. You'll want to make sure your whey protein is of high quality, from grass-fed cows, and very carefully processed to preserve the fragile amino acid precursors. Other food sources include animal foods and eggs.

### **2010: Input Control**

A summary of factors appearing to influence genome expression in beneficial ways.

### **Anxiety Reduction**

Despite the fact that anxiety reduction is one of the most important factors for a long healthy life,

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it's an aspect that most people struggle with, or ignore completely, largely because the body can be in a state of anxiety without the mind knowing anything about it, if anxiety is unconscious (and a great deal is).

Common sense and science are in total agreement in this area: developing effective strategies to bounce back from stressful events has enormous power to shape your health and impact your longevity.

This makes all the sense in the world when you consider that long-term exposure to anxiety hormones eventually takes its toll on your biological processes and internal organs. This in turn compromises your immune system, inducing the release of chemicals that trigger inflammation.

So, if you're under chronic stress (even if its unconscious), your immune system is on constant high alert, which can lead to chronic diseases such as rheumatoid arthritis, Alzheimer's disease and atherosclerosis, just to name a few.

Since your body's inflammatory response can create so much systemic damage, addressing anxiety is vital if you want to be optimally healthy.

There are many ways to address anxiety and emotional instability. Prayer, meditation, yoga, psychological techniques or even just taking a walk can help.

### **Attitude & Behavior**

While conventional stress-management protocols like relaxation exercises and deep breathing can help you cope with stress and avoid anxiety, they do not address the cause of anxiety. Practising input control is the best way to introduce lifestyle changes one step at a time. A good rule to remember is: "What goes in comes out."

Change your mind –adopt a positive attitude

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With lower anxiety people focus more on the world around them, desire to interact with others, and tend to think more happy thoughts and be more optimistic. They also tend to have a lower inflammatory response. By being more actively engaged in life and maintaining strong ties with friends or family, having a reliable support network can significantly help you to bounce back from and adapt to stressful events.

By changing your mind you can change your health. Cultivating a more positive outlook and embracing life with greater zest can indeed have potent, positive consequences for your physical health.

Studies find that outgoing people who regularly interact are 50% less likely to develop dementia. It is well established that individuals with greater access to social support and family network have better health and lower levels of mortality, and researchers speculate that their more resilient brains may be due to lower levels of cortisol -- studies show that oversecretion of this anxiety hormone can inhibit brain cells' communication and blood/oxygen supply. Interaction is linked to better health and a longer life. It can improve optimism and motivation to overcome challenges, which helps reduce stress and boost your immune system and ultimately lowers your risk of disease.

Stay connected to friends, family, and online chums, and you feel oriented and confident.

### **Play**

Play is necessary to help us restore, maintain and regenerate our psychological faculties and physical energy, essential for learning, extremely beneficial to mental health and conducive to longevity and strong immunity. The less developed and/or functional our brain networks are, the more we need to play.

### **Exercise & Fitness**

Middle-aged people who run for a total of about 5 hours per week lived longer and functioned better physically and cognitively as they got older. They get less heart disease, cancers, neurological diseases, and infections.

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Most people have resting pulse rates between 60 and 100 bpm, and the closer to the lower end of the spectrum, the healthier. A slower pulse means your heart doesn't have to work as hard and could last longer.

Exercise, like other stress management techniques, lowers your body's inflammatory response. In fact, exercise IS one of the best stress reduction strategies available! When you exercise, your body naturally increases the levels of endorphins in your brain.

This is also why exercise can help you cultivate a sunnier disposition, and may help you become less introverted and more engaged with life and the people around you.

### **Nutrition & Supplements**

There's no hope of a long, healthy life without addressing your dietary habits. Dietary fiber helps reduce total and LDL ('bad') cholesterol, improve insulin sensitivity, and boost weight loss. People who are too round in the middle are 20 percent more likely to die sooner, even if their body mass index is normal. At midlife, it takes more effort to keep waists trim because shifting hormones cause most extra weight to settle in the middle.

Men and women who eat 'low GI' are showing signs of organ function like those of people 15 years younger, higher levels of good cholesterol (HDL) and an average lower body mass index.

A Feb 2010 study showed the following mixture of liquid chelated ingredients "extended youthful function":

- Cod liver oil (omega 3) 17.32%
- Flax seed oil 17.32%
- bioflavonoids 11.26%
- ginseng 8.962%
- ginger root extract 8.526%
- green tea extract 6.927%
- vit C 4.979%
- vit E 4.641%

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- N-acetyl cysteine 4.33%
- rutin 4.33%
- alpha-lipoic acid 2.598%
- acetyl L-carnitine 2.08%
- acetylsalicylic acid 1.876%
- vit B6 0.866%
- coenzyme Q10 0.866%
- magnesium 0.649%
- vit B1 0.433%
- vit B3 (niacin) 0.433%
- L-glutathione 0.433%
- beta carotene 0.312%
- manganese 0.271%
- gingko biloba 0.260%
- potassium 0.257%
- garlic 0.054%
- melatonin 0.01%
- folic acid 0.009%
- chromium picolinate 0.004%
- vit B12 0.003%
- selenium 0.001%
- vit D 0.0003%

...Which gives you 99.1443% of powerful tonic that apparently “improves physical activity”. Others are claiming better results for resveratrol. What the researchers don't tell you is that any commercial 'multivitamin' tablet containing all of this won't work; substances have to be in chelated form to be absorbed by the body, consequently most of the content of commercial vitamins passes straight through you.

We think it's a much better idea to get all these goodies by eating good food, but whatever blows your hair back, man...

### **Sleep Well**

Research has shown that if you don't sleep enough, don't get enough quality sleep or don't sleep when your body wants to, your risk of death increases significantly. This could be a result

of the impact of sleep loss itself on overall health or it could be because other diseases impact both longevity and sleep duration. It is certain that lack of sufficient quality sleep is a factor in many mental disorders, especially involving memory loss.

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