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COVER STORY

Pathways of Aging



Science has not yet found a way to keep us young forever. But there is good news! The latest research on aging reveals that, though we cannot actually stop the ravages of time, we may be able to slow them down.

Experts now know that it is not simply inherited genetics that determines who will live the longest in an energetic, disease-free state. By the time humans reach the age of 80, behavioral choices become significant determinants of a person's overall health and longevity.¹

The article you are about to read examines the mechanisms behind growing old and explains new ways in which aging humans can slow this devastating process.

There is no single cause of growing old, but the various mechanisms that characterize aging are often interrelated. The good news is that scientists are identifying many of these interrelated pathways of aging. This provides those of us alive today with an unprecedented opportunity to gain at least partial control over this devastating process.

For the past 20 years, scientists have focused on free radicals as a culprit in the development of age-related diseases. New research provides a basis that links free radicals with other pathological changes that cause cellular malfunction or mutation (i.e., cancer).

As we age, the body generates higher levels of free radicals and other oxidants.² Unfortunately, antioxidant defenses do not generally rise to meet this challenge,³ remaining either constant or in some cases declining. For example, cells generate more of the oxidants superoxide and hydrogen peroxide, while levels of the key cellular antioxidant glutathione decline progressively with age.⁴

Studies show that the life spans of animal species are affected by their levels of oxidant generation. The higher the level of oxidant generation in a species, the shorter will be its average life span. When scientists engineer cells of *Drosophila* (fruit flies) to increase production of the antioxidants superoxide dismutase (which quenches the superoxide radical) and catalase (which neutralizes hydrogen peroxide), the flies live longer and their metabolic potential increases.

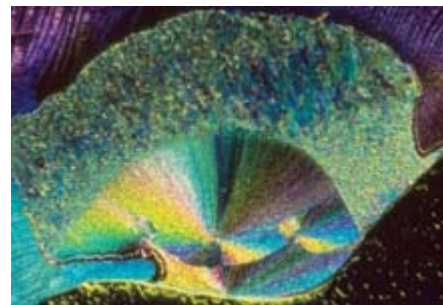
How Free Radicals Deplete Cellular Energy

Cellular function and communication are strictly regulated by a series of enzymatic reactions that occur every second. The age-related decline of our cellular enzyme systems plays a significant role in mitochondrial energy depletion and the subsequent development of degenerative disease.

Scientists have identified age-related decreases in three enzymes that regulate both oxidation and cellular energy production (cellular respiration). These enzymes—cytochrome c oxidase, NADH dehydrogenase, and succinate dehydrogenase—regulate three of the five steps in the process by which cells oxidize food to generate energy in tiny organelles called the mitochondria. The age-related decreases in the activity of these enzymes, which occur in a wide variety of mammalian species including humans,⁵ are believed to play a role in age-related increases in oxidation.

In a fascinating study on rats, supplementation with acetyl-L-carnitine restored cytochrome c oxidase to the level seen in young animals.⁶ This same study showed that acetyl-L-carnitine treatment rejuvenated an important component (cardiolipin) of the mitochondrial membrane that resulted in the restoration of cytochrome c oxidase activity.

Cellular energy generation in the mitochondria is both a key source and key target of oxidative stress in the cell. One can therefore envision a model whereby the inevitable increased production of free radicals compromises mitochondrial efficiency, and eventually energy output, in a detrimental feedback loop.⁷ Yet supplementation with acetyl-L-carnitine enhances mitochondrial



Glutathione crystals. A naturally occurring tripeptide composed of the amino acids glutamic acid, glycine, and cysteine, glutathione is an important antioxidant.

membrane efficiency by restoring a critical antioxidant enzyme (cytochrome c oxidase) to youthful levels.

Lethal Consequences of Cellular Energy Deficit

One adverse consequence of aging is an inadequate energy supply in the cell. Energy-deficient cells lack the minimum metabolic capacity necessary to carry out an orchestrated cell-removal program known as “apoptosis.” The result is that the body’s system for the orderly disposal of defective cells cannot operate. When apoptosis fails, the two alternative pathways the damaged cell takes are highly deleterious. The cell either continues to malfunction and reproduce, or dies violently through necrosis in which the cell swells and ruptures, organelles disintegrate, and inflammation tends to occur.⁸

Scientists long ago discovered that acetyl-L-carnitine and coenzyme Q10 help protect against cellular energy deficits by maintaining healthy mitochondrial function. With new evidence showing a vicious cycle of cellular energy depletion causing more damaging free radicals, and the increased free radicals then causing more cellular energy depletion, the importance of nutrients that boost endogenous antioxidants such as alpha lipoic acid becomes much more apparent. Alpha lipoic acid increases glutathione levels within our cells.



Protein Degradation Initiated by Free Radicals

Another pathway to aging involves the accumulation of proteins with toxic carbonyl groups. Carbonylation results from protein oxidation and reactions of proteins with sugars, aldehydes, and lipid peroxidation products.⁹⁻¹¹

Protein carbonylation increases with age, damaging about one-third of the body’s proteins later in life.^{10,12} These dysfunctional proteins accumulate in vital organs, clogging the cellular machinery just as the buildup of sludge clogs an automobile engine until it seizes. Carbonylated proteins are visible in aging skin and cataracts. Their destructive effects on cellular function underlie diverse age-related conditions, from neurodegeneration, cardiovascular disease, and kidney failure to the chromosomal instability that leads to cancer.

New research shows that as yeast cells age through succeeding cell divisions, a threshold is crossed that dramatically increases chromosomal instability, thereby increasing genetic defects by a multiple of 40 to 200.¹³ Chromosomal instability is a prerequisite for tumor development and increasingly is recognized as a driver of age-related degeneration. The authors of the yeast study point out that mutation rates increase with age, while the risk of developing cancer increases more than tenfold in humans from age 40 to age 70. They postulate that the accumulation of age-related damaged proteins thwarts the cell’s sensors for detecting DNA damage. Thus damaged proteins prevent cells from repairing damaged DNA or activating an orderly cell-death program. Consequently, damaged cells survive and reproduce, leading to mounting genetic, and in particular chromosomal, instability.

Copper Damages Brain Cells

The “transition metals,” especially copper and zinc, catalyze key reactions that “carbonylate” proteins. These metals are neurotoxic at levels far lower than previously thought, as demonstrated by new research findings that trace amounts of copper in the drinking water of rabbits induces accumulation of amyloid beta and formation of the insoluble senile plaques, which are hallmarks of Alzheimer’s disease.¹⁴ Moreover, these metals catalyze the most destructive protein-denaturing processes, protein glycation and the subsequent formation of advanced glycation end products (AGEs). Glycation results from protein-sugar reactions that cause tissue, like chicken in the oven, to brown and lose elasticity. Further copper-catalyzed reactions cause glycated proteins to irreversibly cross-link and ultimately form AGEs, which generate free radicals that in turn stimulate AGE formation in a vicious circle. Glycotoxins present in cooked food add to the body’s AGE load, with higher cooking temperatures and longer cooking times increasing the food’s AGE levels.¹⁵



Glycation Harms Arteries, Eyes, and Kidneys

Advanced glycation end products accelerate aging processes and promote degenerative disease. A new study in subjects without apparent cardiovascular disease demonstrated that plasma AGE levels correlate with subclinical atherosclerosis and carotid arterial plaque.¹⁶ AGEs are associated with impaired vascular reactivity in non-diabetic subjects. A study of kidney disease patients shows that plasma AGE levels correlate with red blood cell deformability, which in turn correlates with vascular disease and retinopathy.¹⁷ This adds to earlier reports of correlations between plasma AGE levels and impaired kidney function.

The best ways to protect against protein degradation, copper-zinc brain toxicity, and chromosomal instability will be discussed later in this article.

The “Sugar” Connection

Everyone with glucose-handling difficulties is at increased risk of developing life-threatening conditions ranging from heart disease

and stroke to blindness, nerve damage, depression, and kidney disease. These dire complications are the result of hyperglycemia (excess glucose in the bloodstream). There is now evidence that those with high “normal” fasting glucose levels suffer a greater incidence of disorders that are associated with diabetic conditions.



According to the American Diabetes Association, diabetes affects about 17 million Americans. Some medical professionals believe this figure may vastly underestimate the true scope of the pandemic. An additional 16 million are suspected of having a precursor condition known as prediabetes.¹⁸ When prediabetic patients are accounted for, the legions of people at risk of developing serious diabetic complications swell alarmingly. Taken together, known diabetics and prediabetics—collectively described as having “glucose-handling” difficulties—represent a shocking 12% of the entire US population. Alarmingly, diabetes was listed as the sixth-leading cause of death on death certificates in 1999, and records suggest that this figure may grossly underestimate diabetes’ actual contribution to deaths. And the statistics are not improving. To the contrary, the ranks of diabetics are swelling along with our collective girth.

The Insidious Progression of Diabetes

The public is largely unaware of the insidious manner in which type II diabetes destroys tissues throughout the body. Only recently have some physicians recognized the magnitude of damage that occurs in the prediabetic state, and how early intervention can reverse this course before “full-blown”

diabetes manifests.

Our understanding of type II diabetes and its related disorders, such as impaired glucose tolerance and impaired fasting glucose, is undergoing a radical change, particularly as data suggest that the risk of complications commences many years before the onset of clinical diabetes.^{19,20}

Type II diabetes was previously regarded as a relatively distinct entity. Doctors waited until fasting blood glucose levels were consistently above 126 mg/dL before taking steps to reduce the excess glucose. Little else was done to address the multiple complications associated with the diabetic state.

We now know that the impaired ability to efficiently handle glucose, progressing all the way to full-blown type II diabetes, is often a manifestation of a much broader underlying disorder.²¹ This includes the metabolic syndrome (sometimes called Syndrome X), a cluster of cardiovascular risk factors that includes visceral obesity, increased propensity of blood to abnormally coagulate, and loss of protein in the urine, in addition to impaired glucose tolerance.



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This new paradigm relating to type II diabetes also influences contemporary therapy for the disease. Evidence now exists for a far more-aggressive approach to treating not just hyperglycemia, but also other cardiovascular risk factors such as hypertension, elevated LDL/triglyceride levels, low HDL levels, hormone imbalances, and central obesity in type II diabetic patients. The objective with multimodal therapies is to significantly reduce cardiovascular morbidity and mortality. While this is a worthy objective, chronically elevated glucose levels inflict damage to other parts of the body, which few doctors take steps to prevent.

To further complicate matters, the cells lining the blood vessels in diabetics suffer from a functional deficiency of thiamine, for reasons that are not yet fully understood. In essence, the very molecule (thiamine) that could help avert hyperglycemia-induced damage is itself broken down by the highly reactive molecules that are created in response to hyperglycemia. This catch-22 situation would appear to be cause for despair.

As discussed in this month's "As We See It" column ("What You Don't Know About Blood Sugar"), aging people with high "normal" fasting glucose levels also may be at risk for complications relating to sugar toxicity.

Slowing These Destructive Processes

All is not lost, however. Recently, scientists have begun taking a closer look at benfotiamine, a compound derived from thiamine. Used for more than a decade in Germany to treat nerve pain in diabetics, benfotiamine is fat soluble and therefore considerably more available to the body than thiamine.^{23,24}



A landmark new study, published earlier this year in the medical journal *Nature Medicine*, found that benfotiamine increases transketolase activity in cell cultures by an astounding 300%. By comparison, when thiamine was added to cell cultures, transketolase activity increased a mere 20%. This robust activation of transketolase by benfotiamine was sufficient to block three of the four major metabolic pathways leading to blood vessel damage. Additionally, benfotiamine blocked activation of the pro-inflammatory transcription factor NF- κ B. This suggests yet another beneficial attribute of benfotiamine.²⁵

The study research team, based at the Albert Einstein College of Medicine of Yeshiva University in New York, further demonstrated that benfotiamine prevents damage to blood vessel cells cultured under hyperglycemic conditions in "test tubes" in the laboratory. Similarly, benfotiamine completely prevented retinal damage in live laboratory animals. "The data...indicate that treatment of diabetic patients with benfotiamine or other lipid-soluble thiamine derivatives might prevent or delay the development of diabetic complications," concluded the authors.²⁵

One of the team's researchers is reportedly applying to the US Food and Drug Administration for permission to begin human trials of benfotiamine as a new drug. Although promising drugs do not always work as well in human subjects as they do in laboratory animal models, researchers are confident that benfotiamine will at the very least prove safe in humans. It has, after all, been used successfully in Germany for more than a decade to treat diabetic neuropathy, with no reported side effects.²⁴

Small studies on human subjects conducted in Europe also show tantalizingly positive results. A study on human subjects in Hungary found that six weeks of benfotiamine treatment resulted in significant improvements in diabetic polyneuropathy in 93% of cases. Polyneuropathy is a painful condition that results when diabetes damages nerves in the extremities. The research team found benfotiamine therapy to be both safe and effective.²⁶

Working along the same lines, a Bulgarian research team enrolled 45 diabetic patients in a three-month observational study to determine the efficacy of benfotiamine for the treatment of diabetic polyneuropathy. One group was given benfotiamine while the control patients received conventional B-vitamin supplements. The benfotiamine-supplemented patients experienced statistically significant relief of their pain symptoms, while patients taking vitamin supplements experienced no such improvement. Researchers noted that their results "underscore the importance of benfotiamine tablets as an indispensable element in the therapeutic regimen of patients with painful diabetic polyneuropathy."²⁷ They further noted that benfotiamine therapy resulted in no adverse reactions.



Given benfotiamine's excellent, decade-long safety record among European patients, it seems safe to predict that even the most

skeptical of clinicians will eventually be convinced that benfotiamine is both safe and effective for the treatment of dangerous diabetic complications. As patients' waistlines—and numbers—continue to grow in the US and throughout the developed world, it appears certain that benfotiamine will win increasing numbers of fans.

Protecting Against Glycation and Carbonylation

The most effective natural inhibitor of protein carbonylation is carnosine, a dipeptide (the union of two amino acids) present at relatively high levels in muscle, heart, and brain tissue. Carnosine levels, however, decline with age. Carnosine reacts with and removes the carbonyl groups in glycated proteins.^{28,29} Moreover, carnosine suppresses the multiple pathways that lead to protein carbonylation. Carnosine's anti-carbonylation mechanisms include chelation (sequestration) of copper and zinc, quenching of reactive aldehydes and lipid peroxidation products, and scavenging of hydroxyl radicals, superoxide, and the peroxy radical. Carnosine inhibits glycation and especially AGE formation more effectively than the European pharmaceutical amino-guanidine (which is not available in the US), without toxicity. Carnosine's copper-chelating ability, which is instrumental in AGE inhibition, is 625 times more potent than aminoguanidine.³⁰

Several studies show that carnosine prevents protein cross-linking and AGE formation. In particular, carnosine inhibits the cross-linking of amyloid beta, which forms the senile plaques characteristic of Alzheimer's disease.³¹ Carnosine protects neurons from the toxic effects of copper and zinc, which modulate synaptic transmission. In a recent double-blind, placebo-controlled study, carnosine improved the functioning of children with autistic spectrum disorders who were considered untreatable. After eight weeks on 400 mg of carnosine taken twice a day, the children showed statistically significant improvements on all measures in the Gilliam Autism Rating Scale. No children discontinued the study due to side effects. The authors suggest that carnosine may work by improving function of the neurotransmitter GABA through chelation of copper and zinc.³²

Maintaining Youthful DNA Structure

A study of oxygen-induced chromosomal damage reinforces the connection noted earlier between protein carbonylation and chromosomal instability. Carnosine and several antioxidants were tested for their ability to protect cells exposed to 90% oxygen from chromosomal damage. Only carnosine exerted significant protection, reducing the level of chromosomal damage by two-thirds.³³

Carnosine also prevented DNA fragmentation in liver cells exposed to hydrogen peroxide, an oxidant that is pervasive in the body, as well as in cells exposed to the tumor promoter TPA. The authors note the potential of carnosine in apoptosis-related disease, including neurodegenerative diseases such as Alzheimer's and Parkinson's.³⁴

Not only does carnosine rejuvenate cells—helping to keep skin and connective tissue supple and elastic, which gives skin a more youthful, wrinkle-free appearance and preserves muscle strength and vitality—but it also protects heart muscle from oxidation, thus warding off heart disease.

Studies suggest that AGE-inhibitors like carnosine may generally become promising drug treatments for Alzheimer's disease and even Parkinson's disease,^{31,34} and also may prevent further injury and death in patients who have undergone coronary angioplasty.³⁵



In prediabetes, a patient's blood glucose levels are abnormally elevated, but not enough to warrant a diagnosis of type II diabetes. Prediabetes can be subdivided into two precursor conditions: impaired glucose tolerance and impaired fasting glucose. Although these conditions are believed to be reversible if addressed in time, most prediabetic patients experience few if any symptoms, and thus have no idea that they are at risk of developing diabetes. That is why it is so important to guard against sugar toxicity before a diabetic state manifests.

How Sugar Damages Cells

The problems associated with higher-than-desired sugar levels are myriad. Most stem from the central problem of excess glucose flooding into blood vessel cells. Fortunately, one of the body's own enzymes, transketolase, is known to block the absorption of too much glucose. But to do its work, transketolase, requires the B vitamin thiamine as a cofactor. Unfortunately, thiamine (vitamin B1) is water soluble, which makes its less available to cells. Initial experiments have shown that the addition of thiamine to cell cultures bathed in excess glucose boosts the effects of transketolase, but only marginally.²² This suggests that scientists were on the right track, but that a thiamine derivative with better bioavailability might be needed to do the trick.

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Carnosine Extends Animal Life Span

Carnosine may appropriately be called an agent of longevity; in animal studies it extended the life span of senescence-accelerated mice by 20% on average compared to mice that were not fed the supplement, and doubled the number of mice who lived to old age. The researchers concluded that, in addition to extending the lives of the mice, carnosine significantly improved their appearance, physiological health, behavior, and brain biochemistry.³⁶⁻³⁸

Unfortunately, our natural levels of this important dipeptide decline with age; muscle levels, for example, are reduced 63% between the ages of 10 and 70, which researchers speculate may explain why our muscles tend to decline in both mass and function as we age.³⁹ And although we can replenish some of the carnosine we need by eating meat (a main dietary source of the dipeptide), with so many of us cutting back on this source of protein today, taking a carnosine supplement is often necessary.

Guarding Against Hormone and Immune Decline

Our neuroendocrine and immune systems declines as we grow older, and laboratory studies suggest that this may cause these systems to send inflammatory chemical signals that contribute to cell death or senescence—and may even have an effect on life span.⁴⁰

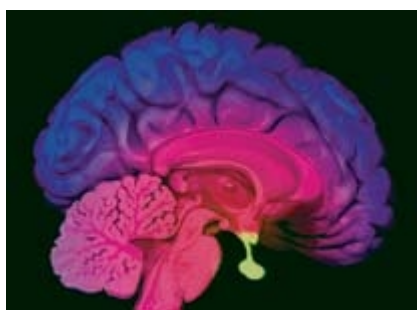
Moreover, as we age and our neuroendocrine systems stop working at peak performance, there also is a decline in levels of the essential polypeptide hormone insulin-like growth factor 1, or IGF-1 (also called somatomedin C).^{41,42} IGF-1 circulates in the blood to each cell in the body, coordinating cellular function and regulating cell growth and division.

What exactly is IGF-1? When human growth factor, or HGH (often called the “Fountain of Youth” hormone) enters the blood stream from the pituitary gland, it is taken up by the liver and converted to IGF-1, which binds with cells throughout the body, including the brain, exerting a growth effect. IGF-1 is in fact responsible for many of the age-defying effects attributed to HGH—and a decline in IGF-1 is thought to result in a reduction of cell activity.⁴³



Research shows that IGF-1 increases insulin sensitivity and lean body mass,⁴⁴ reduces fat, and builds bone, muscle, and nerves,^{45,46} which is why it can reverse many of the physical signs of aging. These include loss of muscle strength, mass, and endurance, sagging skin and wrinkles, uncontrolled weight gain, joint pain and inflammation, decreased energy, loss of flexibility, and digestive problems. Researchers say that one of IGF-1's greatest benefits, however, is its ability to repair peripheral nerve tissue that has been damaged by injury or illness.

Shortages or imbalances of IGF-1 are now thought to be a key factor in the aging process and in the development of aging-related health woes such as Alzheimer's disease,⁴⁷ type II diabetes (and its complications such as diabetic retinopathy), Syndrome X (aka metabolic syndrome), arteriosclerosis and heart disease,^{45,48-50} and Lou Gehrig's disease,⁵¹ as well as difficulties recovering from surgery and trauma. Recent research has revealed that higher levels of IGF are not a factor in the development of prostate cancer, as previously speculated.⁴³



A three-dimensional MRI showing a normal brain, highlighting the pituitary gland and the pituitary stalk (yellow).

Within the last four years, researchers have associated low IGF-1 levels with beta amyloid, the putative cause of Alzheimer's disease,⁴⁷ amyotrophic lateral sclerosis/Lou Gehrig's disease,⁵¹ ischemic heart disease⁴⁹ and carotid atherosclerosis in elderly men.⁴⁹

In a newly published study,⁵⁴ hypertensive patients were followed to determine their risk of developing carotid atherosclerosis. Multiple logistic regression analysis revealed that insulin-like growth factor binding protein 3 (IGFBP3) level was associated with a ninefold higher risk of carotid plaque formation compared to LDL cholesterol or IGF-1 levels. It can be inferred that low levels of free IGF-1 are a risk factor for this disease.⁵²

In a study of asymptomatic subjects infected with HIV-1, the hypothesis that oral administration of three grams per day of acetyl-L-carnitine could significantly affect IGF-1 levels was tested. The researchers found that while acetyl-L-carnitine did not raise total IGF-1, it significantly increased levels of free IGF-1 (the bioactive component of total IGF-1) in the treated patients. The researchers stated that none of the subjects investigated reported any toxicity directly or indirectly related to acetyl-L-carnitine administration. Remarkably, all the treated patients reported, subjectively and without exception, an

improved sense of well being by the second and third week of acetyl-L-carnitine therapy.⁵³

Finally, a recent study suggested that higher growth hormone/IGF-1 levels in adulthood play a determinant role not only for regressive manifestations (chronic diseases) but also for life potential (longer life span).⁴⁶



Summary

Aging is a multifaceted process. Scientists have found that many of the molecular mechanisms that cause disease and premature aging are interrelated. These interconnected pathways provide a basis for humans to counteract these destructive age-related processes.

We now know that free radical damage directly causes cellular energy depletion, and that these energy-depleted cells then generate more toxic free radicals. Even more insidious is that these energy-depleted cells may not go through normal apoptotic-removal processes, but instead send out signals that attract destructive inflammatory cytokines that in turn damage healthy cells. Energy-depleted cells that fail to undergo normal apoptotic removal become chromosomally unstable and are much more vulnerable to transform into cancer cells. Therefore, a clearly established

mechanism now exists to explain how aging cells are more likely to turn cancerous, in addition to malfunctioning in a way that will eventually lead to debilitation or death.

An increasing number of scientific studies reveal that sugar toxicity is a causative factor in a host of degenerative diseases and premature aging. One only has to look at the multiple diseases suffered by diabetics to appreciate the lethal effects of protein glycation and carbonylation, major complications related to excess sugar (glucose) levels. Non-diabetics also encounter these destructive, protein-damaging glycation and carbonylation processes, albeit at a slower rate than diabetics.

Taking steps to guard against glycation would appear to be a mandatory part of a health maintenance program. Dietary modification and aggressive control of blood sugar levels reduce glycation reactions. For instance, avoiding food cooked at high temperatures appears to reduce the formation of AGEs in the body. Higher blood glucose levels facilitate glycation processes, so keeping blood glucose in lower normal ranges is recommended.

Carnosine and benfotiamine appear to be the most effective nutrients to reduce glucose-induced cellular damage. Carnosine protects against glycation, carbonylation, copper-zinc toxicity to brain cells, DNA fragmentation, and dangerous free radicals. Benfotiamine blocks the absorption of excess glucose into cells and protects against glucose-induced cellular toxicities.

Aging humans accumulate excess body fat, suffer energy deficiencies and occluded arteries, and encounter various forms of neurological impairment. Deficiencies in carnitine play a role in these disorders through multiple pathological mechanisms. Not only has acetyl-L-carnitine been shown to enhance mitochondrial energy function, but it also boosts levels of free IGF-1, a hormone necessary to maintain youthful cellular function throughout the body. As people reduce their consumption of foods high in carnitine, supplementation with bioavailable acetyl-L-carnitine appears to be a prudent way of ensuring optimal daily intake of this important nutrient.

Humans seeking to live a healthy extended life span can take relatively simple steps to protect against today's known causes of premature aging and degenerative disease.



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