HEALTH AND STRESS

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STRESS: CAN IT MAKE YOU AGE FASTER & SHORTEN YOUR LIFE?

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As an old saying goes, "Everyone wants to live long but nobody wants to grow old." Chronological age is easily determined by your date of birth. But how old you are biologically can be quite different and is often difficult to determine. For example, biological age can be assessed by the degree of balding, gray hair, wrinkled skin, cognitive impairment, cataracts, arteriosclerosis, degenerative arthritis and other manifestations of old age. When each of these markers of aging becomes evident differs for each of us, they have no consistent relationship with one other, and may be affected by various inherited, environmental or lifestyle factors. Longevity is largely determined by genetic influences and despite numerous claims, there are no interventions that have been proven to either prolong life or retard the aging process - at least in humans.

We would all like to think otherwise, which is why anti-aging supplements, hormones, caviar creams, botox injections, hair restoration and other rejuvenation therapies brought in close to $45 billion last year. About $38 billion went for supplements and drugs to prevent age related problems with the remainder on products and procedures that promise to make you look younger. The anti-aging market is growing at an annual rate of over 9% and is projected to reach $72 billion within four years. Antioxidant supplements are particularly popular because of purported solid scientific support. Similar claims are made for low calorie and other diets as well as certain electromagnetic devices. Yet, despite animal studies that are often cited, none of the above interventions have ever been proven to help people live longer.

ALSO INCLUDED IN THIS ISSUE

Antioxidants, Hormones, Restricted Calorie And Other Diets

Anti-aging medicine advocates claim they can slow, stop or even reverse the aging process by administering specific antioxidant supplements, herbal concoctions or hormones alone or in combination. Most scientists subscribe to the theory that arteriosclerosis, gray hair, cataracts and other

manifestations of aging are due to damage from free radicals. These are oxygen byproducts resulting from normal metabolic activities that lack one or more electrons, which makes them unstable and highly reactive. When produced in large amounts, free radicals race around the body robbing electrons from healthy cells that causes injury to cell walls leading to the creation of more free radicals, setting up a chain reaction. Antioxidants help to prevent this just as they are used to stop foods from spoiling and retard deterioration of rubber or rusting in metals due to oxidation. Free radical oxidative damage is normally blocked by antioxidants such as superoxide dismutase and glutathione as well as hormones like estrogen, testosterone, DHEA and melatonin. Unfortunately, as we grow older and especially after age 55, our ability to manufacture these natural antioxidants starts to decline sharply.

Studies show that people who eat adequate amounts of antioxidant rich fruits and vegetables have less coronary disease, cataracts and even certain cancers. However, each plant can have hundreds of chemicals containing various combinations and amounts of vitamins and other antioxidants and it is not known which factors provide these protective effects. No studies in humans have shown that taking megadoses of antioxidant vitamins C, E, A or beta-carotene alone or in combination help prevent cancer or coronary disease. Lung cancer prevention trials found that beta carotene could actually increase risk, especially for smokers and those who also took vitamin E had a higher incidence of stroke. A recent *Lancet* review similarly reported that antioxidant vitamin supplements were associated with an increase rather than decrease in the likelihood of developing gastrointestinal malignancies. Vitamin E is popular because its antioxidant activities are believed to reduce risk of cancer and coronary disease. However, a study published in the March 16 issue of the *Journal of the American Medical Association* reported that patients who took vitamin E supplements for about 7 years did not have less cancer or cardiovascular events and there was actually an increase in heart failure. Growth hormone, testosterone, estrogen and progesterone have been shown in clinical trials to improve some of the physiological deficits associated with old age but may also have adverse side effects. **The bottom line is that no hormone, vitamin or other nutritional supplement alone or in combination slows human aging.**

All sorts of anti-aging diets are also being promoted, one of the most popular consisting of foods consumed for centuries by Europeans living around the Mediterranean. This diet is characterized by a high intake of vegetables, fruits, and cereals, a moderate to high intake of fish, a low intake of saturated fats but high intake of unsaturated fats (particularly olive oil), a low intake of dairy products and meat - and a modest intake of alcohol, mostly as wine. Studies show that this type of diet is associated with a decreased incidence of heart disease and that people living in Mediterranean countries like Spain and Italy can expect to live longer on average than people in other countries. This was confirmed in a report on 75,000 men and women over the age of 60 from nine European countries just published in the *British Medical Journal.* Their diets were carefully rated with respect to the degree of similarity to the Mediterranean diet and there was a clear correlation between high coherence and longevity, especially in Greece and Spain. In Italy, the majority of deaths were in the North, where the diet was quite different.

The only diet that has been shown to significantly retard aging in animals is one that severely restricts total calories. Scientists believe that the reason caloric restriction slows down aging is that it reduces free radical production and subsequent mitochondrial damage from oxidative stress. A leading proponent of this theory was Dr. Roy Walford, Professor of Pathology at UCLA School of Medicine, who believed

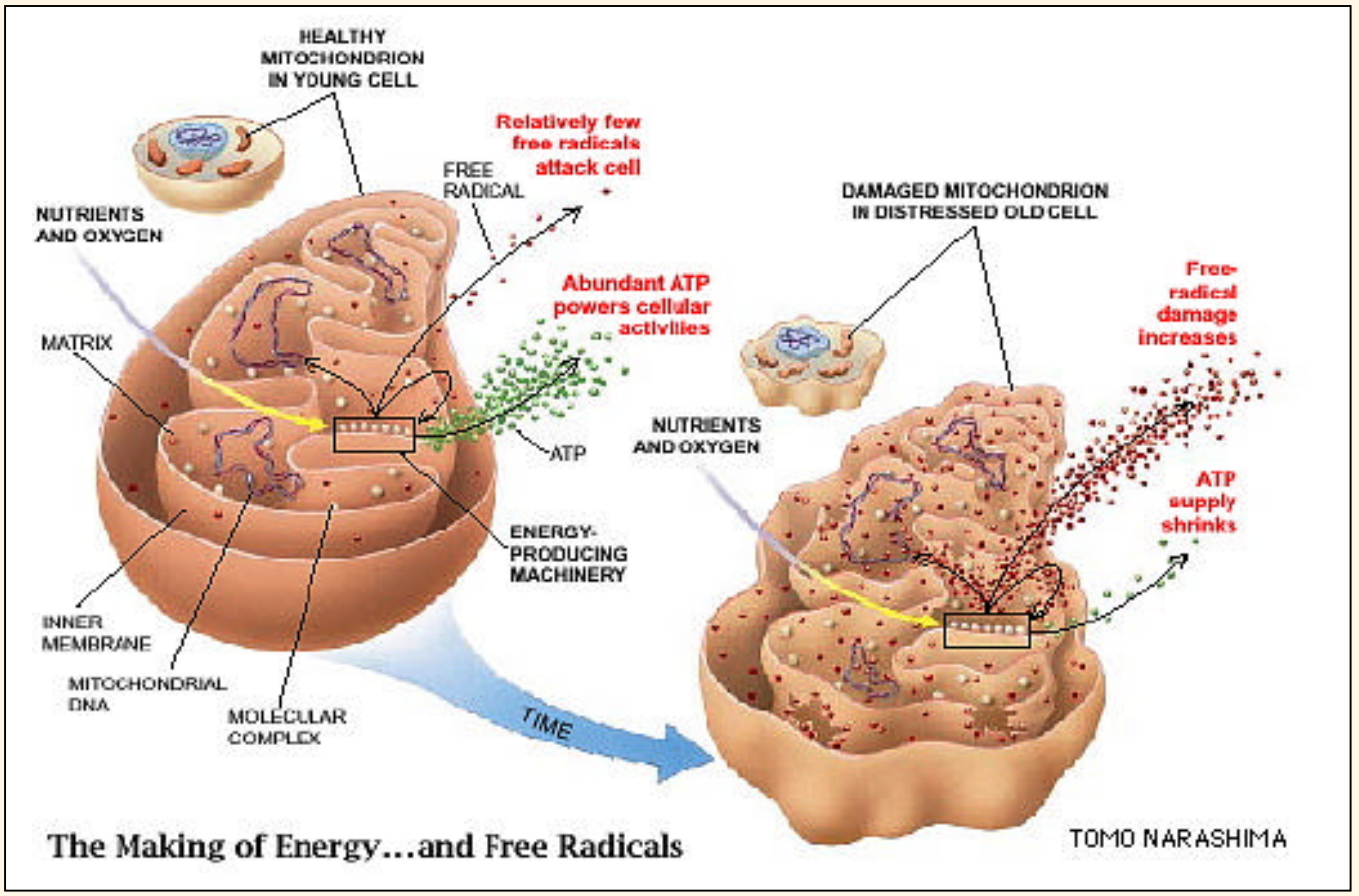
that cutting back on calories could allow people to live to 110 or 120. Walford showed that he could increase the average 39-month life span of mice to 54 months if he cut their normal caloric intake by 40 percent. Furthermore, his calorie-restricted mice retained good intellectual and physical function and at 36 months could run a maze with the same facility as a 6-month-old normally fed control. Walford was so impressed that he adhered to a 1500 calorie diet for almost two decades during which he maintained his weight at 130 and had no appreciable decline in physical strength or mental agility until he developed and died from Lou Gehrig's disease at age 71. No studies have yet shown that caloric restriction prolongs human longevity.

Biological Clocks, Telomeres And The Magic Of Mitochondrial ATP

How healthy we are and how long we live may be affected by lifestyle factors like smoking and exercise but heritable influences can also play a major role. Not much is known about biological clocks containing the genetic material responsible for determining longevity but one of these time keepers that is being intensively studied are the telomeres located at the ends of chromosomes. Telomeres act like the plastic tips that protect shoelaces from unraveling, but they wear away every time a cell divides. As we grow older and cells have divided many times, chromosomes progressively shorten as their telomeres disappear. Telomere length appears to determine the life span of connective tissue and blood cells and is much shorter in senior citizens compared to people in their forties or fifties. When telomeres vanish completely the DNA at the tip of the chromosome is no longer protected and the cell cannot replicate itself and dies. Although cancer cells divide very rapidly they do not self-destruct because they produce telomerase, an enzyme that can restore and regrow telomeres. For example, the life span of corneal cells grown in tissue cultures is similar to that seen naturally. However, when telomerase is added to the culture the cells keep dividing and replicating over and over as long as telomerase is made available. However, it is not likely that telomerase or anything else that prevents telomere shortening will prove to be a fountain of youth or lead to immortality. Brain, heart, kidney and muscle cells never divide so their telomeres don't get shorter or determine their longevity.

It has also been proposed that biological aging results from an inability to repair or replicate DNA due to deficiency of helicase, another enzyme that protects DNA from damage. Helicases are molecular motor proteins that can convert chemical energy into mechanical work. One of their functions is to separate (or unzip) two strands of DNA so that they can be repaired or replicated. Insufficient or defective helicase is associated with increased malignancies and progeria disorders in which relatively young individuals appear prematurely aged. One example is Werner's syndrome, which is characterized by accelerated aging and is four times more common in males compared to females. Patients suffering from Werner's syndrome have graying and thinning of their hair, infertility and testicular atrophy in their thirties and almost all require surgery for bilateral cataracts by the age of 40 if they live that long. The incidence of cancer is also higher in these individuals. What role various helicase enzymes may play in normal aging is not clear but is also an area of intensive investigation.

A more promising approach is based on the mitochondrial theory of aging. Mitochondria supply the power for all cellular activities by converting the chemical energy from foods into a usable form through the formation of adenosine triphosphate or ATP. When this molecule is broken down, the energy stored in its powerful phosphate bonds is released for the cell to use for making hormones, enzymes, reproducing itself or any other purpose.



(From Caloric Restriction And Aging, *Scientific American*, January 1996)

As indicated, most scientists believe that aging results from the destructive effects of free radicals, shown above in red. Free radicals are formed when the energy producing machinery in the mitochondria (boxed in black) utilize oxygen and nutrients to synthesize ATP. These radicals attack and can permanently damage not only the machinery but also other portions of the mitochondria including the DNA on the mitochondria's chromosomes that contain the instructions on how to make ATP. As noted to the right, the accumulated mitochondrial damage over time causes a decline in ATP production as well as an increase in free radical damage to other components so that cells are starved for energy and die. If one mitochondrium dies another must divide to replace it but the new mitochondria may have mutations. As this occurs over and over accumulated mutations appear throughout all of the replicated mitochondria so that they do not function normally and energy production eventually becomes seriously impaired. Some have likened this to the telephone game where a short phrase is whispered to a child in a circled group of classmates who then turns to the next person and whispers what he thought he heard and this is again repeated to the next child. By the time the message is passed around the circle and the last child repeats the phrase it is often corrupted because someone either didn't whisper it clearly or didn't hear it correctly. Similarly, each time the mitochondrial cell reproduces itself new DNA errors may arise that further interfere with optimal ATP production. If enough "DNA debris" accumulates the cell will be depleted of energy and cease to function.

Sirtuins, Red Wine, Heart Disease And The Remarkable Resveratrol

Few people would be willing to relinquish the pleasures of dining and savoring some fine wine for the unproven promise of a few additional years. However, if we knew more about how caloric restriction retarded aging it might be possible to achieve the same

results with a pill that stimulated or mimicked the mechanisms that were responsible. That's not as far fetched as it seems. A decade ago, MIT researchers found that stimulating a silent information regulator gene (SIR2) could extend the life of a brewer's yeast colony. They also discovered that when the yeast colonies were given less food, they lived longer. The underlying mechanism seemed to be that starvation stimulated the SIR2 gene. None of this seemed to apply to humans until a recent Johns Hopkins study reported that SIRT1, the mammalian version of this gene, was also turned on when mice were put on a calorie-restricted diet. Activating this gene stimulated the production of enzymes called sirtuins that protect cells from damage and prolong their life. Further proof of their crucial role comes from studies showing that the life-extending benefits of calorie restriction are not seen in animals that had been genetically altered to lack sirtuins.

Now the race is on to find compounds that are potent sirtuin stimulators to fool the body into thinking it's living on a radically calorie-reduced diet, in effect allowing people to still eat their cake and live longer. Sirtris, co-founded by Harvard's David Sinclair has already identified several chemicals that double sirtuin production and prolong life in worms and fruit flies and has raised $45 million to verify similar results in mice and monkeys. Proving anti-aging benefits in humans is difficult because such trials would take decades so the immediate objective will be to slow the progression of age related disorders like Alzheimer's and coronary disease. One of the most promising compounds is resveratrol, which has been shown to increase the longevity of yeast cells up to 70 percent by boosting SIRT2. Resveratrol is found in high levels in grape skins and since its concentration in wine depends on how much time the skins are present during the fermentation process, levels are much higher in red wine than white wine or other products like grape juice. Various studies suggest that moderate consumption of red wine appears to reduce deaths from coronary disease. This is particularly true in France, where the intake of saturated fat is higher than in other European countries but the incidence of coronary disease is among the lowest. This "French Paradox" is thought to be due to the fact that the French have the highest per-capita consumption of wine in the world.

Recent resveratrol research helps to explain this as well as why only **8% of the French are obese compared to over a third of Americans**. Resveratrol also increases SIRT1 in mammals and one study found that SIRT1 could reduce the development of new fat cells and increase the metabolism of fat within existing fat cells by repressing proteins that regulate fat storage during severe calorie restriction. This may have been an evolutionary adaptation for the body to sense short term starvation and counter it by increasing the burning of stored body fat. As the senior author of one report explained, "When cells were exposed to resveratrol, our studies showed a pretty dramatic reduction in the conversion to fat cells and a lesser but still significant increase in the mobilization of existing fat, or the rate at which the cells metabolized stored fat. This clearly could be one of the explanations for the health benefits that some researchers believe can be linked to moderate red wine consumption."

There has been an explosion of interest in resveratrol in the last few years with well over a thousand scientific papers proposing that this miraculous molecule is a potential cure for cancer, heart disease, Alzheimer's and age-related brain disorders, and much more. Resveratrol has been reported to inhibit fungal infections, raise HDL (good cholesterol), increase immune defenses, preserve red blood cells, prevent blood clots and inhibit inflammation. It lowers PSA levels that are a marker for prostate cancer and studies in rodents and cell cultures have shown that resveratrol inhibits the growth of 18 different malignancies ranging from cancer of the ovary and pancreas to leukemias and lymphomas. Unlike chemotherapy drugs that affect normal as well as cancer cells, resveratrol not only does not damage healthy cells but also actually protects them.

Resveratrol also benefits patients who have sustained serious brain or spinal cord trauma and stroke. In these situations the resultant inflammation intensifies the problem, which is why such patients are often treated with anti-inflammatory drugs like prednisone or aspirin. Researchers recently reported that when administered immediately after trauma, resveratrol reversed the signs of inflammation following spinal cord injury in experimental animals just as effectively as prednisone but with better protection from free radicals. It also seems likely that regularly taking resveratrol supplements would significantly reduce brain injury due to a stroke or trauma and this has also been demonstrated in animal studies. One of the more serious complications of free radical damage is hardening and thickening of arteries from inflammation and scar tissue. Resveratrol's antioxidant action helps to block free radical injury but it also opens arteries by enhancing nitric oxide effects. Nitric oxide allows blood vessels to "relax," which increases blood flow. In a recent animal study, a high-cholesterol diet decreased nitric oxide by about a third and resveratrol significantly reversed this response. In most of the above instances it only required about 3 to 5 milligrams daily from three or four glasses of red wine of resveratrol to get beneficial results. One study reported that "Among men who consumed four or more 4-ounce glasses of red wine per week, we saw about a 60 percent lower incidence of the more aggressive types of prostate cancer." No such effect was seen with hard liquor, beer or white wine, which has 90% less resveratrol. As one researcher asked, "How much more could one ask of one molecule?"

However, another warned, "It would be very premature to suggest that supplements of resveratrol would have any benefits, because this compound oxidizes very quickly and easily loses its metabolic effectiveness. Because of that we have a hard time even studying it in a laboratory setting." The reason is that during the wine making fermentation process resveratrol extracted from the skin of a red or purple grape is kept in a nitrogen-flushed bottle that prevents oxidation from exposure to air. Grape skins provide resveratrol, but not in the active extracted form found in red wine because of oxidation and the same is true for grape juice and sun-dried raisins. Resveratrol is a natural antifungal substance made by grapes and other plants. How much resveratrol is contained in a glass of wine depends on numerous factors including whether the grapes were grown organically, where they were grown, how much time the skins are present during fermentation, how the wine was made and the type of grape. Grapes sprayed with pesticides to prevent fungal infection contain very little resveratrol. Wines grown in dry climates have less resveratrol than those grown in humid areas and white wines contain the least because grape skins are removed early during the fermentation process. Pinot noir grapes grown in northern climates like New York, Washington and Oregon are said to have more than twice as much resveratrol as cabernet sauvignon or Merlot but muscadine grapes from the Carolinas also got high grades.

In addition to grapes, resveratrol is also found in various vines, pine trees, peanuts, and other plants, particularly the giant knotweed plant (*Polygonnum cuspidatum*). This is also known as *fo-ti* in Asian cultures and China, where it is an ingredient in traditional medicines that have been prescribed for liver and heart conditions for centuries. In Japan, a variety of knotweed plant is used to make Itadori tea, a traditional remedy for heart disease and stroke. **However, these plants do not contain the same type of resveratrol found in red wine, which remains the only reliable source of the biologically active compound.** Tests conducted by Harvard researcher David Sinclair, a leading authority on resveratrol's ability to stimulate sirtuin production and Cornell's Leroy Creasy, a professor of plant science, **failed to find any significant biological activity of resveratrol in dietary supplements including tablets, capsules or liquid herbal extracts, most of which contain knotweed plant. Compared to wine, Creasy claims it would take thousands of capsules of these supplements to provide the equivalent amount of resveratrol found in a glass of pinot noir.** The reason is that

encapsulation fails to duplicate the airtight environment found in a wine bottle, which preserves the resveratrol. A new technology bankrolled by Pfizer is now able to seal dietary supplement ingredients in an airtight gelatin pill with a nitrogen bubble to retard oxygenation. It has been utilized in an attempt to produce the first stabilized red wine extract with biological activity but positive results have not yet been reported.

Nevertheless, various red wine and resveratrol capsules containing knotweed plant extracts are already making anti-aging as well as numerous health claims based on the research cited above despite the fact that they have no or little biologically active resveratrol. However, since they are classified as nutritional supplements, there is little that regulatory authorities can do. As previously noted, a similar problem exists with other supplements like Cortislim that promise to promote weight loss by reducing stress and cortisol despite no studies that support such asinine claims. This problem does not exist in Europe and other countries that have adopted the Codex alimentarius regulations, which might well be mandated in the U.S. in the next few years. Last year, the prestigious Institute Of Medicine asked Congress for additional FDA funding to insure dietary supplement safety and the power to pull products that could not prove their claims.

Heredity, Methuselah, Indy, Other Anti-Aging Genes And Exercise

There can be little doubt that hereditary factors have a major influence on whether you will live to an exceptionally old age. Iceland has unique birth and death records going back to Viking ancestors and deCode Genetix researchers in Reykjavik reported that individuals who lived to be over 90 were much more likely to be related compared to controls with average life spans. Since many of these super seniors were still living and the company has a bank of blood samples from 60,000 inhabitants used to identify genes that predispose people to schizophrenia, asthma, and osteoporosis, they wanted to see whether they could pinpoint genes that promoted longevity. Two such genes were subsequently identified; one of which they labeled the Methuselah gene after the Biblical character who allegedly died at the age of 969 and also had long-lived ancestors. This gene also appears to be linked to fertility and according to the Bible, Methuselah "begat Lamech" when he was 187, who had Noah at the age of 182 and lived another 595 years during which he sired more children. deCode is attempting to determine the gene's exact DNA sequence and has received funding from several sources to develop drugs that might replicate its actions.

Harvard researchers had previously reported that 100% of the centenarians they studied had Methuselah-type genes that also protected them from age-related conditions like dementia, heart disease and cancer. Siblings were four times more likely than controls to reach 90 and their children lived 10 -15 years longer than the norm. Brothers and sisters of centenarians also had half the mortality rate of other people born at the same time from age 20 all the way into extreme old age. Brothers had a 17-fold greater chance of living to 100 and the sisters had an 8 times greater likelihood. In 1994, The New England Centenarian Study under the direction of Thomas T. Perls began to investigate centenarians living in the greater Boston area but now includes others in the U. S. and abroad. One of the most significant findings has been that 90% of centenarians remain functionally independent up until an average age of 92 years. Almost a third had no change in thinking abilities or other cognitive functions and disorders common in the very elderly so that the gene also appears to slow down biological aging. With respect to fertility, many centenarian women have a history of bearing children after the age of 35 years and some were over 40. Studies show that a woman who has a child by natural means after the age of 40 has a 4 times greater chance of living to 100 compared to others who give birth in their twenties. From an evolutionary perspective, it has been suggested that this is because women who give birth after the age of 40 need to live longer to take care off their offspring. It now seems more likely that this merely reflects

that their reproductive organs are aging more slowly as are various other structures and systems in their bodies.

After studying some 330 centenarians in 137 families, Perls and his group have strong evidence that at least one important longevity gene that also provides resistance to disease is located in a small region of chromosome 4. They formed Centagenetix, a biotechnology company that is now studying over 1500 people and significant progress has been made in delineating the gene on chromosome 4 that validates earlier studies. Centagenetix subsequently merged with Elixir Pharmaceuticals, co-founded by Leonard Guarante of MIT, who first discovered that calorie restriction stimulated the SIR genes that promote longevity, regulate fat metabolism and reduce heart disease. The new entity is actively seeking to expand its intellectual property base with "patents covering sirtuin structure/mechanism and downstream activators/pathways" and has attracted significant funding from three large venture capital firms. Last September, Elixir obtained a patent entitled "Identifying Lifespan-altering Agents" which describes methods for identifying agents that extend life span and protect against stress. They had previously become the exclusive licensee for a patent entitled "Genetic Loci Indicative of Propensity for Longevity and Methods for Identifying Propensity for Age-Related Disease" in anticipation of their ability to discover products to prevent and treat age-related disorders and complaints.

Connecticut researchers have also discovered that mutating or blocking a gene at another site can double the life span of fruit flies. They named this gene Indy (I'm Not Dead Yet) based on a quip in the movie *Monty Python and the Holy Grail*. In addition, **long after normal flies have aged and died, the mutated Indy flies continue to eat as much, mate vigorously, lay as many eggs, and retain their youthful energy and endurance**. The DNA sequence of the Indy gene is very similar to a gene in humans responsible for pumping the preliminary products of food metabolism into cells where they are further processed. In mutant Indy flies, this pumping is interfered with so that less metabolic energy is obtained from food. The Indy mutation seems to be the genetic equivalent of putting the flies on a severe calorie restricted diet but it allows them to eat as much as normal and maintain their strength and stamina until they die. Scientists are actively searching for a **drug that could inhibit a human Indy gene that theoretically might allow you to enjoy good health up to age 120 or possibly longer**.

With respect to the significance of heredity, a woman in Kansas named Helen Boley is the only known person to have the Methuselah gene inherited from both sides of her family. **When she was born, 7 of her great-grandparents were still alive and all her grandparents lived to their late 90s or into their 100s** even though they had only one copy of the gene. Boley's own resistance to disease was attributed to extraordinarily low LDL cholesterol and an unusually high level of HDL. However, it is not known whether these are merely markers associated with Methuselah gene activity rather than the mechanism by which its benefits are mediated. A similar tendency was reported in over 300 Ashkenazi Jews with an average age of 98 being studied at the Longevity Genes Project at New York's Albert Einstein School of Medicine. These elderly Jews and their offspring tend to have a mutation in the gene for cholesteryl ester transfer protein (CETP), which shifts cholesterol molecules from HDL to LDL. Inhibiting CETP raises HDL levels and 25% of the centenarians had a variant that blunted CRP activity compared to only 8% of controls. Clinical trials with drugs to block CETP are underway with torcetrapib (Pfizer) and JTT-705 (Roche) and Aventis is developing a vaccine designed to have the same effect. The Ashkenazi centenarians also had lipoprotein particles that were exceptionally large, a phenomenon usually only seen in young adults who exercise very vigorously. Whether these large particles are related to longevity is not clear, although regular exercise is believed to be associated with a longer as well as healthier life.

How Does Stress Speed Up Biological Aging?

It is doubtful that stress can turn your hair gray overnight but its ability to accelerate aging is readily illustrated by photographs of Presidents before and after serving a four-year term. In addition to numerous other anecdotal reports, animal and laboratory studies also confirm that stress can accelerate the aging process. A vivid illustration is provided by the Pacific salmon and the Atlantic eel since during their relatively short spawning periods biological age increases significantly. They die shortly after spawning, and exhibit adrenal cortical hyperactivity and other characteristic pathologic changes that are associated with being subjected to severe stress. This is undoubtedly due to the tremendous emotional strain and physical exertion required to swim upstream against rapids, since if spawning is prevented, both of these fish continue to live for several years. In books directed to the general public, Hans Selye later redefined stress as "the rate of wear and tear on the body", which is also a fairly accurate definition of biological aging.

Longer-lived animals usually have higher genetic resistance to environmental stressors such as heat, cold, oxygen deprivation or starvation. This increased resistance is due to the presence of "heat shock" proteins that are present in all cells in all life forms. They are also called "stress" proteins since they are produced in response to protein-damaging stressors. Without these protective agents organisms die sooner because of diminished resistance to infections and free radical damage. The link between stress resistance and longevity is further strengthened by studies showing that manipulating the genes that make these protective proteins can extend lifespan. When researchers generated a line of fruit flies genetically altered to overexpress these heat shock or stress proteins their lifespan was extended by 30%, and they also exhibited increased resistance to various stressors. Similar genetic manipulation produced the longest lifespan ever achieved in roundworms and according to the lead author of one study, "**In human terms, these animals would correspond to healthy, active 500-year-olds**." The search is now on for drugs that might stimulate the production of natural heat shock or stress proteins.

University of California researchers recently showed for the first time a clear correlation between psychological stress and a cellular indicator of aging in healthy people. They studied 39 women aged 20 to 50 who had been experiencing persistent stress for years because they were caring for a child suffering from cerebral palsy, severe autism or some other serious chronic illness. Stress level ratings were compared with those of 19 other very similar women whose children were healthy and biological aging was evaluated by measuring telomere and free radical activity. Female caregivers that were more stressed, as gauged by their subjective ratings and/or the duration of their ordeal, showed more signs of premature aging. The longer a woman took care of a sick child, the shorter the telomeres in her white blood cells and women who felt the most stressed also had lower levels of telomerase, the enzyme that restores telomere length. In addition, they had greater evidence of cell damage due to "oxidative stress". **Those women whose subjective ratings of stress were the highest had the equivalent of 10 years of extra aging in their immune cells compared with women in both groups who rated their stress lower.**

As indicated, most stigmata of old age result from the cumulative effects of free radical oxidative damage. Some studies have shown that 15 minutes after the onset of emotional distress there is a significant rise in LDL oxidation due to increased free radical production. Stress also causes atrophy of the hippocampus and loss of memory and cognitive skills that are identical to those seen with aging that result from free radical damage. Perl's Harvard study of centenarians also reported that their ability to deal with stress played an important role in living a longer as well as healthier life. Centenarians showed a marked variation in years of education, socioeconomic status, religion, ethnicity as well as dietary patterns, which ranged from strictly vegetarian to very high in saturated fats. Obesity or a

substantial smoking history was rare but what they did have in common seemed to be a superior ability to cope with stress. This was often facilitated by a good sense of humor. In "Living to 100", Perls noted,

> "Centenarians are natural stress-shedders, but what comes easily to them because of their innate personalities may have to be consciously learned by the rest of us. . . Myer Saxe, a 100-year-old man who rose from newsboy to owner of a large shoe factory, attributes his abilities to shed stress not to an easy-going personality but to a conscious decision at a certain point in life that he was going to be a 'fun guy'. 'I decided not to worry about anything I saw that worrying didn't do any good'. With their stress-resistant personalities and low risk for neuroticism and depression, centenarians are natural stress-shedders who shrug off life's slings and arrows with relative ease. If people can emulate centenarians, either through stress reduction programs, alternative approaches like yoga, or a regular physical exercise program, we believe they stand a much better chance of coping with the mental and physical problems of old age."
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> "Some survival strategies of the centenarian lifestyle are unexpected. One of our centenarians' most effective self-protective devices comes from their ability to lighten their emotional load with humor. Many older people become sensitive about discussing illness, sex, and the prospect of death, or become preoccupied with troubles. In contrast, a visible and consistent component of the centenarian repertoire is humor."

Centenarian Stress, Shakespeare, Swift And The Struldbruggs

Some centenarians can expect to live another decade or possibly even two. Jeanne Calment is believed to have been the world's oldest person whose birth date could be officially validated. She was born in Arles, France on February 21, 1875 and recalled meeting Vincent Van Gogh in her father's shop. When she passed away in 1997 she was documented as having lived 122 years and 164 days and attributed her longevity to a good sense of humor, Port wine, chocolate and lots of olive oil. She rode a bicycle to the age of 100 and smoked until she was 120 years old. Her doctor said that she stopped because of pride rather than health concerns - "she was too blind to light up herself, and hated asking others to do it for her." She is said to have remained spirited and mentally sharp until the end but spent the last 12 years of her life in a retirement home, confined to a wheel chair, blind and nearly deaf.

It should be emphasized that although many centenarians lead active lives they all become disabled by the time they reach 110 because they are deaf, blind, demented and/or unable to get out of bed on their own. There are now more than 60,000 people in the U.S. over the age of 100 and that number could approach 1 million by 2050 since age 80 and over is the fastest growing segment of the population. And if any current research efforts should pay off and some magic anti-aging pill or treatment protocol were to be developed, the

total number of such super seniors could be staggering and a serious strain on medical resources since most would be disabled. Things are not very different now than they were over 400 years ago when Shakespeare's description of the Seven Ages of Man ended with

"... ... ... Last scene of all,
That ends this strange eventful history,
Is second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything."

The pursuit of immortality or eternal youth has been a recurrent theme since the medieval legend of the Wandering Jew, the alchemist's search for the "Elixir of Life", Ponce De Leon's quest for the "Fountain of Youth" and Christopher Marlowe's *Dr. Faustus*. *Gulliver's Travels*, published in 1725, was a satirical commentary on eighteenth century society that allowed Jonathan Swift to criticize such things as corruption, vanity, class and sex differences and the popular pursuit of immortality. In one of his travels, Gulliver sails to the land of the Luggnuggians where he hears a surprising tale about some of their inhabitants called Struldbruggs, or "Immortals". It was explained that very rarely, a child was born with a red circular spot directly over the left eyebrow, which signified immortality. "The spot grew larger over time and changed its color. When the person was 12 years of age, the spot was green; at 25 years, it turned to a deep blue; at 45 years, it grew coal black and was as large as an English Shilling, and it subsequently remained that color. The children of the Struldbruggs were mortal like others in their society. Immortality was not peculiar to any family but occurred by chance." Gulliver is envious and goes on to enthusiastically describe what he would do if granted immortality, including becoming the wealthiest person in the kingdom, studying the arts and sciences until he excelled all others in learning and "a living treasury of knowledge and wisdom such that I would become the Oracle of the Nation". However, he soon learns that the Struldbruggs' immortality is a curse rather than a blessing.

Grandville's Illustration of The Struldbruggs

"They acted like Mortals, till about Thirty Years old, after which by Degrees they grew melancholy and dejected, increasing in both till they came to Four-score Years . . . which is reckoned the Extremity of living in this Country, they had not only all the follies and infirmities of other old men, but many more which arose from the dreadful Prospect of never dying. They were not only Opinionative, Peevish, Covetous, Morose, Vain, Talkative, but uncapable of Friendship, and dead to all natural Affection, which never descended below their Grand-children. . . . They have no Remembrance of anything but what they learned and observed in their Youth and middle Age, and even that is very imperfect. . . . As soon as they have completed the Term of Eighty Years, they are looked on as dead in Law; their heirs immediately succeed to their Estates, only a small Pittance is reserved for their Support, and the poor ones are maintained at the publick Charge. . . At ninety, in talking they forgot the common Appellation of Things, and the Names of Persons, even of those who are their nearest Friends and Relations. For the same Reason they never can amuse themselves with reading, because their Memory will not serve to carry them from the Beginning of a Sentence to the End; and by this Defect they are deprived of the only Entertainment whereof they might otherwise be capable."

Throughout the course of the book, Gulliver's encounters with each culture signify a progression from a benevolence towards man to disappointment and misanthropy that eventually causes him to go insane. Fourteen years earlier in *Thoughts on Various Subjects*, Jonathan Swift had written "Every man desires to live long, but no man would be old". Swift died at the age of 78, a very long life at the time. The tragedy is that like the Struldbruggs he had written about, Swift became progressively infirm and senile after he reached 60, was declared incompetent in 1742, and died three years later. But suppose some magic potion or procedure was developed that could markedly lengthen your life without any significant loss of physical strength or mental faculties. After all, if genetic manipulation can allow experimental animals to live the equivalent of 500 years, why couldn't we some day enjoy good health until age 150 or more? Would this be desirable?

The fact is that such a population explosion would create all sorts of problems with the availability of resources like food, energy, medical services housing and funding for continued Social Security payments, especially since some predict the system will be bankrupt in a few decades. And if people continued to stay well physically and mentally until they were 120 or older how would younger generations work their way into positions of more authority if previous ones were not forced to relinquish such roles? What would people do with themselves if they lived so much longer? If they knew they were going to live that long would it change their behavior? Would they become more conservative or more adventurous - more or less likely to have kids? We marry for better or worse, but what if you wanted to take the treatment and your spouse didn't? Perhaps living to 120 or more, even if you stayed healthy, might not be such a blessing after all.

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