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CAN STRESS ACCELERATE AGING AND GRAY HAIR?

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As emphasized in previous Newsletters, what determines chronologic age is readily defined as the number of years you have lived, and it is the same for everyone. Biologic age differs for each of us and is difficult to define, since it refers to various age related degenerative changes in different organs and structures that bear no relationship to each other with respect to their appearance, progression, severity or impaired function and quality of life.

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Some of these, such as premature gray hair and certain types of baldness, seem predetermined by genetic factors, and little can be done to prevent or delay their appearance. Others, like muscle weakness, osteoporosis, and hearing loss, which may also have a hereditary component, are more apt to be influenced by aerobic and weight bearing exercises or avoiding chronic exposure to very loud music and noise.

Generally speaking, with the exception of regular exercise, maintaining a nutritious diet, obtaining adequate amounts of sleep and rest or avoiding environmental hazards, it is difficult to delay biologic aging or to promote healthy longevity. In contrast, there are numerous influences that have the reverse effect, and stress is the most pernicious of these when it comes to accelerating biologic aging as well as shortening life expectancy.

Exactly What Does Biologic Age Mean And Can It Really Be Measured?

There are numerous web sites that promise to tell you your biologic age and/or life expectancy based on self report answers ranging from 10 to 150 questions about your medical information, smoking, drinking, driving and other personal habits, family history, geographical location, etc. Some claim to give you answers depending on how many times a week you crave chocolate, the elasticity of your skin when you pinch it, and many include questions about stress that also provide techniques to reduce it. The Stress Sweeper Test from Advanced Wellness Solutions will allegedly "Evaluate your biological age in 1 minute" using their Heart Wizard, which predicts how fast you are aging, what your biological age will be one or two years from now, and which anti-aging techniques are best for you based on your breathing pattern (see www.heartwizard.com). This is based on heart rate variability feedback, as is the Heart Tracker, which will similarly "mitigate the impact of stress, improve mental relaxation, normalize blood pressure, and strengthen the immune system". (See www.biotech.com) However, neither of these and other copycat devices have adequate scientific studies to support their claims, in contrast to heart rate variability devices such as www.emwave.com and www.stresseraser.com featured in prior Newsletters.

A different approach from www.naturalstresstherapy.com (not to be confused with www.naturalstress.com) offers the Cellular Health Test that determines biological age by measuring "cellular vitality and toxicity, body fat, muscle mass, intracellular/extracellular fluid, inflammation" and other "biomarkers of aging." This is sometimes also known as the BIA test, since "it uses bio-electric analysis to conduct an effective measurement of your body's electro-conductive properties and is a preventative tool that can show imbalances in your body composition." The results show what biomarkers need to be improved so that a personal nutrition and lifestyle program can be designed to target them. There are also sites that will measure your true mental and emotional age as well as the biological age of your dog or cat. One "True Age Test" consists of only five questions, the first being "What are your feelings about jokes that involve farts?" with some suggested answers to choose from. This should not be confused with www.trueage.com, which offers various "skincenticals" that rejuvenate the skin and prevent or delay the signs of aging. This site also has numerous links to www.realage.com, far and away the most popular and profitable site for determining biologic age by analyzing responses to its lengthy questionnaire. However, in order to evaluate the authenticity of this approach, it necessary to understand exactly what biological aging really means, since it is comprised of numerous physical, physiological, mental and emotional changes. None of these have any consistent relationship with any other with respect to when they appear, and some of those listed below may never surface.

Physical And Physiologic Changes Associated With Aging

- Increased atherosclerosis.
- Decreased cardiac output and blood flow.
- Increased blood pressure.
- Decreased kidney, liver and pulmonary function.
- Decreased elasticity of blood vessels.
- Loss of muscle mass and strength.
- Increased osteoporosis.
- Increased osteoarthritis.
- Diminished hearing, especially for higher frequencies.
- Diminished sense of taste and smell.
- Cataracts, macular degeneration, arcus senilis.
- Slower reaction time.
- Progressive graying and loss of hair.
- Drier, rougher, more wrinkled, and keratotic skin changes.
- Declining levels of estrogen, testosterone, melatonin, DHEA.
- Impaired immune system responses.
- Atrophy or hyperplasia of cells.
- Increased intracellular pigments associated with degeneration.
- Increased amyloid, calcium and immune complex deposits.

Mental And Emotional Changes Associated With Aging

- Progressive inability to remember recent events.
- Surprisingly improved memory for things well in the past.
- Poorer personal hygiene habits and sanitary standards.
- Lack of attention to appearance and cleanliness.
- Progressive loss of a sense of independence and control.
- Easy fatigability, lack of pep, energy, or "get up and go".
- A more conservative attitude about events and people.
- Feelings of loss of attractiveness.
- Increased feelings of loneliness, and social isolation.
- Tendency to paranoia, depression, and emotional instability.
- Increased concerns and anxiety about possible future health problems, financial insecurity, and having fewer friends.

Self-report responses are notoriously unreliable and more accurate information can often be obtained from family or close friends. For example, Type A's are often unaware of or deny their toxic traits, which are best assessed by observation in an interview designed to elicit them.

The Realage.com Craze And The Phenomenal Success Of "Infomediaries"

In addition, many stigmata of aging are not covered in questionnaires, since they require the results of a physical examination, laboratory tests and imaging procedures that are not always available. Questionnaires provide a picture of health status, but this is not the same as biological or "real" age, nor is it likely to predict life expectancy. These important distinctions have been skillfully blurred by RealAge, a company founded in the mid nineties by Charles Silver and Dr. Michael Roizen. Silver was a thirty-five year old entrepreneur who had a radio talk show and had previously founded a chain of oil change shops in Michigan that was later sold to Jiffy Lube. Roizen, an anesthesiologist and internist at the University of Chicago, was interested in the impact of various influences on health. Along with some colleagues, he reviewed some 25,000 relevant articles and after summarizing the results, developed a test to determine biologic vs. chronologic age based on responses to 124 questions. The company offered this test at no charge when it went on line in 1999 with www.realage.com/. Within a year, over 2 million had taken the quiz that provided data about medical problems and habits on 1.3 million registered users, which was a gold mine for advertisers.

As Silver explained in a 2000 interview, his strategy was to gather this information to help people improve their health, but also to match it with products likely to fit their needs. Users pay no money to become registered members and receive periodic e-mail "recommendations" that are essentially advertisements. Realage.com charged between 15 cents and \$1 for clients to get their message across, depending on how targeted the audience was. Pharmaceutical companies vied to place their preferred position ads for headache, heartburn, hypertension and other drugs that would reach registered members most likely to use them. Co-branding deals were also made with popular websites like oprah.com, women.com, myprimetime.com, thirddage.com, proflowers.com, family.com, Nabisco and other huge companies, as well as insurers like the now infamous AIG. All of these were geared to baby boomers, Realage.com's prime target group. Financial agreements varied. RealAge paid some partners or gave away content free in return for their e-mail client lists and split revenues with others from ads on their sites. Silver also said he believed that "infomediaries", which refers to companies that use the Internet to link advertisers to a very specific and desirable audience, would prove to be the business model of the future.

The rest is history. Since then, the questionnaire has been increased to some 150 questions, most of which appear to have been tweaked to attract more advertising rather than improve the accuracy of the results. It has been somewhat of a sensation in the marketing world due to an explosive growth that supports Silver's prediction. Hearst Magazines paid an estimated \$100 million to acquire the realage.com site in 2007 because its

users are very similar to the audience attracted to their magazines, especially *Redbook*, *Cosmopolitan*, *Good Housekeeping* and *O*, (the Oprah magazine). At the time, it had annual revenues of \$20 million, 2.1 million unique visitors a month, over 8 million registered users, and 17 million had taken the test. Due to aggressive Internet advertising, numerous promotions on Oprah, strong endorsement by Dr. Mehmet Oz, four books by Roizen that topped the *New York Times* best seller list and several co-authored by Oz and others, more than 27 million people have now taken the test. During this process, they are repeatedly asked if they would like a free RealAge membership. If they answer yes to any of the prompts, test results go into a marketing database, which now contains over 9 million registered members. Few people would fill out a lengthy questionnaire detailing all their health and other problems and hand it over to a drug company seeking customers for a new or existing product. But that is essentially what realage.com does.

The company promotes better living through non-medical solutions and works with some 90 consumer product companies to offer healthy solutions to "live life to the youngest", like taking multivitamins, certain supplements, eating breakfast and flossing your teeth. However, the site makes its money by selling prescription drugs via 29 companies in 46 different therapeutic categories that include 72 different brands. Pharmaceutical companies pay RealAge Inc. to compile test results of members who are then selected to receive specific e-mail marketing messages. Data can be used to identify those with symptoms of a disease and send them messages even before it has been diagnosed by their doctors. One company does this to promote a procedure that removes the endometrial lining in post-childbearing, pre-menopausal women with heavy periods that are often due to fibroid tumors. It purchases a list of women in the 37-to-49 age group who then receive a series of e-mail messages explaining why this can be a serious medical problem. The last few suggest their treatment as a possible solution, emphasizing that it is minimally invasive and can be done in a doctor's office in 90 seconds with a ninety percent permanent success rate that avoids the need for a D&C. Drug companies can use any combination of test answers to find whether someone is taking antidepressants, blood pressure drugs, how sexually active they are or even if their marriage is happy to identify prospective customers. As the RealAge vice president for marketing recently said, "At the end of the day, if you want to reach males over 60 that are high blood pressure sufferers in northwest Buffalo with under \$50,000 household income, that also have a high risk of diabetes, you could."

Critics complain that the company's privacy policy does not specifically address their relationship with drug companies. It does state, "we will share your personal data with third parties to fulfill the services that you have asked us to provide to you," and it only adds test results to its database

when respondents become members. But many believe that consumers do not have enough information when they join. As the director of the Health Research Group at Public Citizen, a public interest group in Washington recently noted, "Literally millions of people have unknowingly signed up," and realage.com "can create a group of people, and hit them up and create anxiety even though the person does not have a diagnosis."

Silver is still CEO and Roizen and Oz are on the Scientific Advisory Board but none have any particular expertise in geriatric medicine. Roizen, who now heads Cleveland Clinic's Wellness Institute, has been criticized for claiming that **people could now live to 120 with the quality of life of a 45-year-old and within the next 15 years, they'd be able to live until 150 or 160.** A professor of aging, health, and society at Case School of Medicine and past president of the Gerontological Society of America described these claims as "optimistic, but rather wild exaggerations of what could be accomplished in such a short time frame." In *You: Staying Young*, one of a series of books co-authored with Oz (to whom Oprah Winfrey refers as "America's Doctor"), readers are promised that following the authors' advice will **help them live 35 percent longer, and that 70 percent of aging is affected by simple things you do - or don't do.** Several years ago, 51 leading scientists in the field of aging research published a position paper that denies many of Roizen's claims. For example, it states that exercise and a balanced diet can increase life expectancy by delaying some age-related diseases, but there is "no scientific evidence to support the claim that these practices increase longevity by modifying the processes of aging."

Dr. Jay Olshansky, a professor in the School of Public Health at the University of Illinois and one of the co-authors of the position paper, was appalled at the claim that people would soon live to be 160, stating, "Shame on him. This is the general public and we have responsibility to be honest." He believes it is important to encourage people to lead healthier lives, but that this does not excuse Roizen's "separate, constant misstatements about aging." Olshansky maintains that Roizen makes these claims to sell books, and warns, "As soon as you hear there's an anti-aging doctor in the vicinity, protect your wallet. They are going to try and separate you from your money." Some recommendations have also backfired, such as promoting the health benefits of acai berry on the Oprah Winfrey show, since it was later demonstrated to be an Internet scam. Realage.com also sells, books, DVDs, advice on food and recipes, fitness gear, beauty and rejuvenating skin preparations and a host of health and wellness products, including automated blood pressure devices, emergency radios, smoke alarms, wedge pillows, massagers, brain games, special slippers, hand exercise "stress balls", all kinds of pill containers, and even seat belts for pets.

Does Being President Hasten Gray Hair Due To Increased Job Stress?

Roizen has received a lot of media attention by allegations that increased job stress has accelerated aging in U.S. Presidents. This is apparently supported by the steady growth of gray hair during their tenure, as shown below.



President Clinton 1992



President Clinton 2001



President Bush 2001



President Bush 2009

Looks pretty convincing, but we simply don't know what they would have looked like eight years later if they had been in a more relaxing but less distinguished and rewarding occupation. Roizen believes that Presidents and CEOs age more rapidly because it is lonely at the top. However, although

loneliness and social isolation are associated with adverse health effects and increased mortality, there is no good evidence that feeling lonely will turn your hair gray. There is little doubt that a hectic schedule of daily travel to make multiple public speeches and getting little sleep can take its toll, as illustrated below by pictures of Hillary Clinton before and after her campaign.



Hillary Clinton in 2007



After 2008 campaign

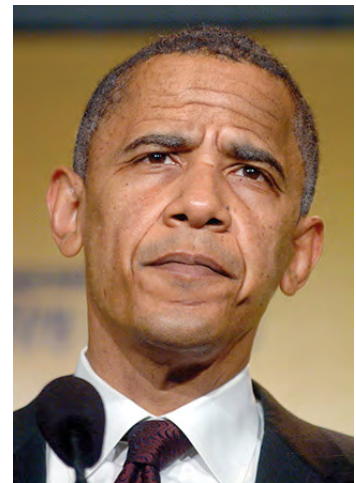
But women usually color their hair, and before and after photos can be influenced by makeup, time of day and "doctoring" after they are taken. The obsession with stress and gray hair recently peaked following President Obama's statement that "Running for president will age you quick. When I started this campaign people called me a young man. They're not calling me that anymore. I'm getting gray hair." Several web sites had commented last fall on how rapidly his jet-black hair had started to turn gray to give him the "salt and pepper" look shown below to the left. The effects of stress seemed so certain that pictures were provided of how he would look in 2012.



President Obama in 2009



In early 2008



Projected for 2012

Some questioned whether Obama had previously dyed his hair and then stopped. Others suggested that he had actually begun to touch it gray to provide an air of wisdom, maturity and seriousness. (This is reminiscent of the old advice that **all doctors should have gray hair and hemorrhoids for that distinguished and constantly concerned look.**) Not so, according to Zariff, who has been giving him "*quo vadis*" haircuts twice a month for 16 years and is still his barber. "I can tell you that his hair is 100 percent natural. He wouldn't get it colored." He admitted that the president had developed "a few strands" of gray over the past year but does not appear much grayer now than on Inauguration day. And while the stress of the presidency might be weighing on Obama, "I don't think we should worry about it that much. It hasn't affected his basketball game. He still can shoot some hoops. If it was a whole lot of gray very quickly, I would've noticed it." Obama's graying is of the flecked salt and pepper variety that waxes and wanes depending on how often he gets a haircut. This is usually every two weeks, although whether it is in Chicago or Washington is not clear.

There is no scientific support for the popular belief that stress can make your hair turn gray quicker than usual, much less become completely white overnight from a severe fright. Since hair is a dead tissue, it cannot change color and/or become white until it grows out from the roots, which takes weeks. Nor is there any link between gray hair, baldness or facial wrinkling with increased heart disease, and being prematurely gray doesn't mean that you will die sooner than anyone else. Graying of hair is caused by an accumulation of hydrogen peroxide that blocks the synthesis of melanin, the natural pigment that gives hair its color. All hair cells make tiny amounts of hydrogen peroxide that is converted to oxygen and water by enzymes like catalase and especially Msr (methionine sulfoxide reductase) antioxidants.. These enzymes, which decline with age, also promote the formation of tyrosinase, another enzyme that produces melanin in hair follicles. Thus, because hydrogen peroxide levels steadily increase while levels of protective enzyme levels are progressively decreasing, hair is essentially bleached from within so that it turns gray, and eventually white.

There is no evidence that stress increases hydrogen peroxide production, although one study did show that smokers were four times more likely to become prematurely gray than non-smoking controls. The graying process increases as we grow older to different degrees that primarily depend upon genetic and ethnic influences. For example, whites tend to gray quicker, often as early as their mid-30s, followed by Asians and then Africans. Since about half of 50-year-olds are at least 50 percent gray, 47-year-old Barak Obama actually appears to be doing better than average.

Are All Claims To Extend Or Restore Youth More Hype Than Hope?

Some people believe that embryonic stem cells, resveratrol, telomerase activators, severe caloric restriction or increasing mitochondrial energy production can significantly delay or possibly even reverse certain signs of biologic aging. Adult blood forming stem cells, used in bone marrow transplants for over 40 years to treat leukemia, lymphoma and other hematological disorders are currently the only stem cells commonly used to treat human diseases. The clinical potential of other adult stem cells has also been demonstrated for diabetes and advanced kidney cancer. Geron recently received FDA clearance for the first clinical trial of cells derived from human embryonic stem cells to treat patients with thoracic spinal cord injuries.

There is little doubt that stem cell therapy can benefit patients with specific diseases, but that does not mean they will retard biologic aging. Last month, Korean researchers began a study to evaluate the ability of stem cells to affect the aging process in dogs at least 12 years old, based on improvement in hearing, arthritis, reactivity to external stimuli and tissue regeneration. However, it seems doubtful that the results will have clinical relevance for anyone under the age of sixty.

Resveratrol is making headlines because it appears to increase the lifespan of human cells by reducing damage due to oxidative stress from dangerous free radicals. It initially attracted attention almost two decades ago when *60 Minutes* featured an interview with Dr. Serge Renaud from the University of Bordeaux to discuss why the French had significantly lower rates of heart disease compared to the U.S., despite their high intake of saturated fats. This phenomenon was first noted in 1819 by the Irish physician Samuel Black, and is particularly impressive in people living in the Gascon region of Southwest France. Although they consumed more saturated fat per capita than any other region in the world, incidence of coronary disease was extremely low. Serge, who by coincidence had studied under Hans Selye, called this the "French Paradox." As he told us in a prior presentation at our annual Congress in Switzerland, "goose and duck fat are slathered on bread instead of butter, people snack on fried duck skin, **eat twice as much foie gras as the rest of France, and fifty times more than Americans.**" Many were also heavy smokers. Several explanations were offered to explain their surprising longevity and freedom from heart disease, such as more leisurely dining habits with family and friends and less stress in general.

Serge agreed, but as he told *60 Minutes*, he believed that their liberal consumption of red wine was more important, since it contained chemicals, that reduce the stickiness and aggregation of platelets that can cause clots, as well as several other powerful antioxidants. In addition, as Louis Pasteur had noted, **"Wine is the most healthful and hygienic of all beverages."** Red wine sales promptly skyrocketed and the FDA was petitioned to permit

distributors to claim that red wine promoted cardiovascular health. (Oat and bran cereals had been allowed to do this based on meaningless cholesterol lowering effects.) Others were quick to get on the bandwagon. Grape juice manufacturers claimed their products provided the same benefits and were safer, as did companies selling nutritional supplements containing red wine pressings. Vintners and breweries cited studies showing that white wine and beer provided similar or even better cardioprotection. Distillers promptly pointed out that it didn't make any difference what kind of alcohol you drank and that hard liquor was just as beneficial.

However, red wine was deemed superior, when resveratrol was later found in very high concentrations in the skin of red grapes and appeared to be the ingredient most likely responsible for red wine's benefits. Resveratrol made headlines in 2007 when it was shown to prevent overfed mice from gaining weight, improve their physical performance without exercising, and seemed to slow down biologic aging. Subsequent studies suggest that resveratrol also prevents and reduces insulin resistance and type 2 diabetes, may prevent breast cancer by blocking harmful estrogen metabolites, and more recently, can help repair chromosome damage. Resveratrol is a polyphenol antioxidant made by certain plants to resist bacteria and fungi, and these varied benefits are achieved because resveratrol activates the Sirt1 gene to make large amounts of its SIRT 1 protein that blocks free radical damage to cells. SIRT 1, a member of the sirtuin family of enzymes, has also been shown to increase the formation of new mitochondria, the source of energy for all cell functions, and to improve the energy of existing mitochondria. In addition, it prevents apoptosis, or programmed cell destruction due to age related progressive loss of telomeres, which are little caps at the ends of chromosomes that prevent damage when cells divide. These protective telomeres can also be preserved by telomerase, an enzyme that declines as we grow older, but at different rates depending on what genes we inherit. Emotional stress is also associated with reduced telomerase protection.

Since many manifestations of biologic aging appear to be inherited, is there anything that can be done to prevent them? University of California scientists have already achieved this, at least in worms. The average roundworm is old, flabby, sluggish and wrinkled by the age of 18 days and usually dies a day or two later. However, it is possible to turn them into "mini-Methuselahs" with **life spans of up to 144 days, 7 times longer**, by manipulating one or two genes. In addition, as the lead researcher noted, "You can beat them up in ways that would kill a normal worm—exposing them to high heat, radiation and infectious microbes—and still they don't die. Instead, they're moving and looking like young worms. It's like a miracle—except it's science." These genes reduce the action of insulin and a related hormone called IGF-1 that in turn activates a gene called Foxo,

"which stimulates a whole host of responses that protect cells—boosting the immune system, increasing antioxidants, keeping proteins folded correctly." While worms are far removed from humans, a recent study of Ashkenazi Jewish centenarians found similar genes governing IGF-1, and another found the same protective Foxo gene changes in healthy 95-year-old men.

While we can't change the genes we inherit that govern the production of telomerase and other anti-aging substances, there may be ways to stimulate them or enhance their effects. The TA Sciences' Patton protocol utilizes TA-65™ a molecule that activates telomerase. It consists of an extensive baseline evaluation of 80 specific blood tests that include sophisticated immune system components, six specific aging biomarkers (vascular age, pulmonary function, cognitive status, vision, skin elasticity, bone density) and telomere length measurement. After all these results are evaluated, an office visit or a telephone consultation with a doctor is arranged to discuss the findings so you can decide whether to embark on the program, which is delivered in six month segments separated by two weeks. Every 6 months you will receive a daily supply of TA-65 and complementary basic nutritional supplements. After 6 months, the blood work and biomarkers are repeated, and the results are discussed in a follow-up consultation with a physician to determine if you want to continue with additional six-month treatment segments. The initial testing will set you back about \$3,000 plus \$500 for a medical consultation and each six month treatment module costs \$6,725, in addition to \$860 in laboratory tests, although insurance might cover a few hundred dollars for these. You can discontinue treatment at any time but it is recommended that you try the Patton protocol for at least two years. Unfortunately, you can't buy TA-65 at any vitamin or supplement store if you want to try it out. It is only available at TA Sciences, for \$25,000 a year.

As vividly illustrated in a previous Newsletter, anti-aging has become a very huge and profitable industry. Some products that are heavily promoted, like human growth hormone, are not only ineffective, but also potentially dangerous when not given for approved indications, and the **long-term effects of TA-65 are unknown**. As Elizabeth Blackburn, who received the Lasker prize for discovering telomerase warned, "It will be a long and difficult job to make sure a telomerase drug is safe because **too much telomerase could theoretically boost cancer risks**." Supplements sold in the U.S. can claim anti-aging, stress reduction, improved memory, concentration, energy, immune system function, or anything (other than treating or diagnosing a disease), and proof of efficacy or safety is not required. Nor is there any guarantee that the amounts of the ingredients listed on supplement labels are correct, or are even present. Germany and other countries have strict safeguards to prevent such abuses, and supplements must demonstrate proof of efficacy and safety similar to drugs.

Blackburn recently published a paper showing that **exercise, stress reduction and a low calorie diet can increase telomerase by 30 percent** in men. Strict caloric restriction clearly promotes healthful longevity in animals, including primates, but few humans would choose to live the rest of their lives on such diet. Regular aerobic exercise confers similar benefits, and we have devoted several Newsletters to the anti-aging rewards of reducing stress, although this is more difficult to prove. What is intriguing is that scientific studies of caloric restriction, exercise, telomerase activation, as well as the longevity research in worms, suggest that all of these ultimately stimulate SIRT 1 protein production. Most of the resveratrol and sirtuin research cited has been conducted by Sirtris, which has developed a resveratrol pill that allows overweight mice to run farther and live 20 percent longer, and also prevents weight gain despite a high calorie diet. It is safe in humans, and a trial in untreated diabetics found that it lowered glucose and insulin levels without drugs or any change in diet. They have developed a new SIRT 1 activator that is **1,000 times more potent than resveratrol** in animal studies, and appears to be safe in humans.

It is not surprising that GlaxoSmithKline recently purchased Sirtris for nearly three quarters of a billion dollars. Six other drug companies are also heavily involved in sirtuin research. Until these efforts bear fruit, the safest, most effective and least expensive advice may be to avoid being overweight, get regular exercise, and reduce stress. The latest report on centenarians and their healthy elderly offspring also confirms the anti-aging benefits of strong social support from close friends, having a good sense of humor and lots of laughter. It's also necessary to stay active and productive. **What you retire to is far more important than what you retire from.** The old adage "Use it or lose it" applies for both body and mind. Mental as well as physical exercise are the keys to healthy longevity- so stay tuned to find out why!

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