Anti-Aging Research Bulletin

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1. The Mystery of Aging

Aging is a complex natural process that affects every molecule, cell, organ, and body function. As we age, blood vessels accumulate fatty deposits and lose flexibility, resulting in arteriosclerosis or hardening of the arteries. Production of digestive enzymes declines, resulting in decreased nutrient absorption, and maximum breathing capacity progressively decreases in each decade of life, beginning at about age 20.

But why do we age? Why do some people age faster or slower and in different ways than others? Is there a maximum human lifespan beyond which we cannot live no matter how optimal our lifestyle or other interventions may be? And finally for all of us, the most important question: How can insights into longevity be used to potentially prevent the diseases and disabilities associated with old age, improving the odds that aging will be healthy, active, and independent?

The National Institute on Aging (NIA) explains that gerontologists once only looked for a single, all-encompassing theory to explain aging—a single gene, for instance, or the decline of the immune system—but these experts are now finding multiple processes, combining and interacting on many levels. Cells, proteins, tissues, and organ systems are all involved, and gerontologists are now able to discern many more of the mechanisms by which these components cause or react to aging[1]. As this work evolves and new knowledge accumulates, gerontologists are moving closer to their ultimate goal of promoting optimal health and independence throughout the lifespan.

Although chronological aging is inevitable, unlocking the secrets to “biological” aging is perhaps the ultimate scientific quest. The way cells age, how aging impacts their function, reproduction, and death may help us to better understand the causes and perhaps the solutions for key age-related diseases and conditions.

2. The Epidemic of Aging: Diseases and Disabilities

Many of the diseases that afflict Americans today are diseases associated with aging, and become more severe as we reach our later years. 88% of those over 65 years of age have at least one chronic health condition[2]. Health damaging behaviors, including tobacco use, a sedentary lifestyle, and poor eating habits are major contributors to the nation's leading chronic diseases including arthritis, Alzheimer’s disease, cardiovascular disease, cancer, diabetes, high blood pressure, and osteoporosis[3].

According to the latest available health statistics from the Centers for Disease Control and Prevention (CDC), about three-fourths of all deaths are among persons age 65 and older. The majority of deaths are caused by chronic conditions including heart disease and cancer, which have been the two leading causes of death for persons 65 years of age and older for the past two decades. Stroke or cerebrovascular disease is the third and chronic lower respiratory diseases are the fourth leading cause of death and Alzheimer’s and diabetes are also included in the leading causes of death. CDC indirectly explains that aging can only be healthy, enjoyable and productive if we prevent and control a number of chronic diseases and conditions[4, 5].

According to the US government, the following chronic diseases and conditions are common in the elderly:

Cardiovascular Disease (CVD), primarily heart disease and stroke, causes more deaths in Americans of both genders and all racial and ethnic groups than any other disease. Modifying risk factors offers the greatest potential for reducing CVD morbidity, disability, and mortality, which include high blood pressure, high cholesterol, smoking tobacco, excessive body weight, and physical inactivity. The effects of these lifestyle choices accumulate as one ages, leading to increased prevalence of heart disease and

cardiovascular disease. In fact, the population over age 65 has the highest rates and therefore contributes most to the mounting numbers of deaths each year [6, 7].

Cancer is the second leading cause of death in the United States, causing more than 500,000 deaths each year. Cancer is a group of more than 200 different diseases. and can be generally described as an uncontrolled growth and spread of abnormal cells in the body. The chances of having cancer in a lifetime are 45 percent for men and 41 percent for women. Cancer is largely controllable through prevention, intervention and treatment strategies which can further decrease cancer mortality. The disease becomes increasingly more common with age. As an example, 75% of all diagnosed cases of breast cancer are among women aged 50 years and older [8, 9, 10].

High Blood Pressure is common with about 65 million American adults—nearly 1 in 3—having high blood pressure. Many Americans tend to develop high blood pressure as they get older and middle-aged Americans face a 90% chance of developing high blood pressure during their lives. High blood pressure increases the risk for heart disease and stroke, the first- and third-leading causes of death for Americans. High blood pressure can also cause other problems, such as heart failure, kidney disease, and blindness. The National Heart, Lung and Blood Institute explains that one can control high blood pressure through healthy lifestyle habits and, if necessary, take medication[11, 12].

Diabetes is a group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Diabetes can lead to serious complications and premature death, but people with diabetes can take steps to control the disease and lower the risk. 2007 CDC statistics reveal that 23.6 million people or 7.8% of the population have diabetes, 95% of which is Type 2 diabetes, which develops primarily due to a poor diet and being overweight. In the 60 years of age or older age group, 12.2 million or 23.1% of all people have diabetes. The CDC has reported that one in three Americans born in 2000 will develop the disease[13].

Overweight and Obesity are both labels for ranges of weight that are greater than what is generally considered healthy for a given height. Obesity occurs over time when you eat more calories than you use. The balance between calories-in and calories-out differs for each person. Factors that might tip the balance include a person's genetic makeup, overeating, eating high-fat foods and not being physically active. Being obese increases your risk of diabetes, heart disease, stroke, arthritis and some cancers. According to to the CDC obesity has reached epidemic proportions among Americans of all age groups. In fact, obesity among adults has doubled since 1980[14, 15].

Alzheimer's disease is a chronic, progressive, gradual onset, irreversible condition that destroys brain nerve cells and leads to dementia including loss of memory, intellectual, and social skills. Scientists think that up to 4.5 million Americans suffer from Alzheimer's disease. The disease usually begins after age 60, and risk goes up with age. About 5 percent of men and women ages 65 to 74 and nearly half of that age 85 and older may have the disease. Scientists believe that the disease occurs partly due to the death of nerve cells in the brain as well as lower levels of some brain chemicals[16].

Arthritis is the leading cause of disability in the United States affecting about 46 million Americans (1 in 5). As the U.S. population ages, these numbers are likely to increase sharply. About one third of the people affected by arthritis are 65 years of age and older. The most common form of arthritis is osteoarthritis and another frequently occurring form includes rheumatoid arthritis. Common symptoms include pain and swelling in or around the joints and some forms may even affect multiple organs. Some forms of arthritis are related to overweight and the importance of weight management and physical activity are crucial components of arthritis management[17].

Osteoporosis is common in millions of older Americans and is a disease that decreases bone mass to the point where it leads to increased fracture risk. Osteoporosis is especially common in older women. One out of every two women and one in four men over age 50 will have an osteoporosis-related fracture in their lifetime. In fact, osteoporosis is a major public health threat for an estimated 44 million Americans or 55 percent of the people 50 years of age and older. While osteoporosis is often thought of as an older person's disease, it can strike at any age and can be largely prevented through healthy lifestyle habits and well balanced nutrition[18, 19, 20].

Eye Diseases or conditions in the elderly are cataract, age-related macular degeneration (AMD), primary open-angle glaucoma, diabetic retinopathy, and presbyopia. According to the National Eye Institute, age-related eye diseases and visual loss are common in the older adult population. In 2003, it was reported that almost half of more than 20,000 Medicare recipients developed at least one of three eye diseases (i.e., diabetic retinopathy, glaucoma, or macular degeneration) over a 9-year period. **Cataracts** are cloudy areas in the lens that keep light from easily passing through the lens, causing loss of eyesight. **Glaucoma** results from too much fluid pressure inside the eye. It can lead to vision loss and blindness. If treated early, glaucoma often can be controlled and blindness prevented. **Retinal disorders** are a leading cause of blindness in the United States. The retina is a thin lining on the back of the eye. It is made up of cells that get visual images and pass them on to the brain. Retinal disorders include age-related macular degeneration, diabetic retinopathy, and retinal detachment. The National Eye Institute also explains that research has closely associated visual impairment with fair or poor health status and restricted activity[21].

3. Theories and Mechanisms of Aging: The Ways We Age

Theories abound regarding the biological causes of human aging. They primarily fall into two groups. The programmed lifespan theories hold that aging follows a biological timetable. The wear and tear theories emphasize environmental assaults to our systems that gradually cause things to go wrong[1]. Cells, proteins, tissues, and organ systems all are involved, and the NIA explains that gerontologists are now able to discern more and more of the mechanisms by which these systems cause or react to aging[22]. Prominent cellular and molecular hypotheses of aging are described below:

DNA Damage and Repair
Up to a million DNA damaging assaults occur daily and can be caused by oxidative damage, simple genetic “typos” or mistakes in DNA replication, or even by environmental factors such as radiation or exposure to toxins. These mutations can accumulate, eventually causing cells to malfunction and ultimately die. This process has been suggested as a crucial contributor to the aging process.

Our bodies have repair mechanisms to take care of DNA damage. However, defects in DNA repair seem to be directly related to aging. This critical balance between DNA damage and both protecting the DNA as well as repairing the DNA is an ongoing area of active research into aging.

Genetic Regulators of Aging
Another process that leads to aging and disease is the activation of transcription factors or genetic regulators which interpret the genetic code and control its functional application. Genetic regulators impact a multitude of metabolic processes and events that can lead to cellular dysfunction and aging. They also control the dynamic balance between damage and repair, between energy production and decline, and even cell lifespan.

As years go by, the activity of genetic regulators promoting cell renewal and energy production declines while genetic regulators promoting cell death become more prominent. As natural defenses and self-repair functions decline, cumulative cell damage increases and this cumulative damage contributes to age-related cellular deterioration and diseases of aging, including cancer.

Mitochondrial Aging and Oxidative Damage
Mitochondria are the “intra-cellular power plants” that transform carbohydrates, lipids, and protein into energy but also create toxic oxygen free radicals in the process. They can cause serious damage to mitochondrial membranes and DNA. This oxidative damage can accumulate over time and may contribute to the development of many age-related diseases including cancer, heart disease, arthritis, and Alzheimer’s disease.

Since oxidative damage is associated with so many of the problems associated with aging—lower efficiency of cellular systems, deterioration of tissues, and increased susceptibility to age-related diseases—oxidative damage and its impact on intra-cellular function is a key focus of anti-aging research.

Accumulation of Advanced Glycation End Products (AGE)
With age, our proteins, DNA, and other structural molecules develop damaging cross-links to one another through a process called glycation. Glucose molecules can react with these proteins in the body to form what are called “advanced glycation end products”. The accumulation of these cross-link damaged proteins is tied to the some of the most debilitating effects of aging. In fact, scientists are theorizing that advanced glycation end products may play an important role in development of atherosclerosis, as well as certain complications of diabetes, and chronic renal failure.

Replicative Senescence and Telomeres
Many human cells are known to have a finite capacity of cell divisions before they can no longer divide, a phenomena known as replicative senescence. Many scientists today believe that the length of telomeres, the “caps” found on the ends of all chromosomes, contributes to human aging by limiting the number of times human cells can divide. Each time a cell divides, it reproduces its chromosomes, but it also loses a small bit of its telomeres. When a cell's telomeres reach a critically short length, the cell can no longer replicate its chromosomes and stops dividing. Scientists have generally concluded that while telomeres and senescence may contribute to human aging, they don’t govern it.

Neuroendocrine Dysfunction
The neuroendocrine system refers to the complex connections between the brain, nervous system, and endocrine glands that release their hormones into circulation. There are gradual declines as we age, in production of many of these hormones, including growth hormone, estrogen, progesterone and testosterone. As hormone production declines, changes in neuroendocrine function can result in loss of muscle mass, elevations in blood pressure, impaired sugar metabolism, and sleep abnormalities.

4. Anti-Aging Science: Research Update

Scientists are investing billions of dollars in research on aging. It’s estimated that the National Institutes of Health (NIH) spent over $2.4 billion alone in 2007[23]. Much of the latest research on aging has focused on the following topics:

DNA Damage and Repair
Laboratory studies demonstrate that reducing and repairing DNA damage can have a significant impact on enhancing cellular life span. Polyphenols, natural phytonutrients found in such plants as berries, grapes, tea, olive oil, and cocoa, are recognized for having powerful health supporting properties and recent research has shown certain phytonutrients, including the polyphenol, resveratrol, can modify DNA damage.

When laboratory cells were treated in the presence of select natural compounds, DNA damage was considerably reduced suggesting that resveratrol may be chemopreventive by virtue of its ability to protect DNA as well as to induce DNA repair[24].

Genetic Regulators of Aging
Our bodies have a natural capacity for self-repair and regeneration that can help combat cellular damage and the deterioration that may lead to aging at the cellular level. Activating and favoring key transcription factors or genetic regulators is critical for cellular health, repair, renewal, and longevity.

Plant polyphenols have been shown to trigger key genetic regulators of cellular energy metabolism and longevity which positively impact the cellular aging process. A landmark laboratory study conducted in 2006 by Dr. David Sinclair at Harvard Medical School showed that resveratrol positively impacted the harmful effects of a high fat diet on the heart and liver, insulin resistance, and blood sugar levels, and even counteracted the mitochondrial decline seen with administration of the diet[25].

Genetics and Calorie Restriction
Scientists now believe that genetics may determine up to 35 percent of an individual’s life expectancy as longevity is naturally regulated by specific genes. Although different animal species vary up to 100 times in lifespan, scientists are discovering some surprising similarities between human genes and those of other species.

Specifically, researchers at Harvard Medical School have proposed that specific genes underlie some of the remarkable effects of calorie restriction (CR), which has been shown to delay aging in all species tested, from yeast to primates. In laboratory studies, CR has been shown to prevent many of the diseases of aging including cancer, heart disease, osteoporosis, diabetes and neurodegeneration and some researchers are looking closer at CR research for solutions that can treat the diseases of aging and promote cell survival and longevity. A recent research study confirms that resveratrol may mimic, in mice, some of the effects of dietary or calorie restriction[26].

Mitochondrial Biogenesis and Aging
Optimal mitochondrial function is of paramount importance to maintain cellular energy production and cellular function over time. Laboratory studies indicate that certain polyphenols promote cellular energy biogenesis and help increase production of mitochondrial "power plants" and promote healthy mitochondrial function. In laboratory studies, resveratrol has been shown to exert multiple protective effects against metabolic syndrome through promotion of mitochondrial biogenesis[27].

Furthermore, a review of the many neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis suggests a tight link with mitochondrial dysfunction. New research suggests that resveratrol, could have protective effects in animal models of neurodegenerative diseases[28].

AGE End Product Accumulation and Aging
Recent studies show that certain phytonutrients or polyphenolic compounds can limit the formation of advanced glycation end products (AGE), thus leading to their reduced accumulation, and thereby promoting cellular health and longevity. Resveratrol was shown to significantly inhibit AGE formation and may thereby confer protective effects on the cardiovascular system[29].

The seed and skin fraction of the grape, *vitis rotundifolia*, was examined on AGE formation where both seed and skin extracts were found to be efficacious inhibitors of AGE. This research suggests that consumption of specific grape polyphenols may have some benefit in influencing the progression of diabetic conditions[30].

Hormones and Aging
Hormones are the body's chemical messengers, some of which have garnered special interest from scientists studying the aging processes. While many women with menopausal symptoms are helped by hormone therapy during the menopause transition phase, long-term hormone therapy appears to increase the risk of certain diseases, including heart disease, breast and uterine cancer and hemorrhagic stroke.

There have been a variety of studies looking at the role of growth hormone and DHEA in the aging process. Growth hormone appears to play a role in body composition and maintaining muscle and bone strength as one ages, but for now, there is no convincing evidence that taking Growth hormone injections can improve the health of those who don't suffer a deficiency. DHEA production declines with age but it's unclear if this actually affects the aging process and there may be risks with DHEA supplementation, which has been linked to liver damage in laboratory research[31]. The role of testosterone supplementation is under investigation for preventing frailty, but it remains unclear if supplementation of this hormone has any true benefit outside of treating deficiency.

Exercise and Aging
The sedentary lifestyles of Americans and the effects of inactivity on their health and function are of increasing concern. Researchers are studying exercise as a factor that may be a significant determinant of lifespan. Older persons who engaged in vigorous running and other aerobic activities had lower death rates and slower development of disability compared to those in a more sedentary control group[32].
Elite athletes maintain a high level of fitness throughout their lifespan, but even the performance of elite marathon runners and weight lifters declines after 40 years of age, with peak levels of performance decreased by approximately 50% by 80 years of age. This is dramatic evidence that age-related muscle loss and weakness can be slowed, but not stopped indefinitely[33].

5. Healthy Anti-Aging Lifestyle Tips

Science has proven that many of the chronic diseases and leading causes of death can be prevented or at least controlled, often through simple lifestyle changes. In fact, the NIA emphasizes that achieving and maintaining health and function in advanced years can be aided by a commitment to a lifestyle that promotes fitness, proper nutrition, and avoidance of smoking and other behaviors that adversely affect health. And the good news is that even if healthy habits have been neglected, research has shown that it is almost never too late to begin these habits. Better health habits not only help people live longer, but postpone the onset of disability and compress functional loss into fewer years at the end of life according to NIA's subgoal on *Maintain Health and Function*[34].

Considering independent research findings and recommendations by US government education efforts such as the *Senior Health Initiatives* underscore that adopting the following healthy behaviors will promote better living and a healthy anti-aging lifestyle[35-39].

- **Eat a Balanced Diet**, low in saturated fats and rich in fruits, vegetables and whole grains to have a positive impact on health conditions commonly seen in advancing age.
- **Maintain a Healthy Weight** by eliminating excess calories from your diet and eating nutrient dense vs. high fat or empty calorie foods (especially fast foods) to reduce the risk for many of the diseases of aging. Aim for a BMI of less than 25.
- **Engage in Regular Exercise** including both endurance and weight bearing exercises. Aim for at least 30 minutes of these activities on a daily basis.
- **Increase intakes of Vitamin D** for bone and colon health and to reduce the risk for all cause mortality, **Calcium** for healthy bones, **B Vitamins** to support healthy DNA replication and antioxidant nutrients such as **Vitamins C and E** to address oxidative stress that can lead to cellular aging.
- **Consider bioactive natural phenolic compounds** that may play an active role in supporting a healthy anti-aging lifestyle. **Resveratrol** is a well-studied polyphenol that's been shown to positively impact multiple mechanisms of cellular aging including DNA protection and repair, genetic regulators of cellular aging, and mitochondrial biogenesis thus supporting cellular function and longevity.
- **Get Sufficient Amounts of Dietary Fiber** as eating more fiber might help you avoid intestinal problems and may also lower cholesterol and blood sugar levels.
- **Quit smoking.** It's one of the most effective prevention strategies.
- **Drink alcohol moderately.** Those who choose to drink alcoholic beverages should do so sensibly and in moderation-defined as the consumption of up to one drink a day for women and up to two drinks a day for men.
- **Drink Plenty of Fluids** including water.

Finally, stress reduction, adequate sleep (7-8 hours per night) and regular physical exams, including vision, hearing and dental screening, are also important aspects of a healthy anti-aging lifestyle.

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