Anti-Aging Research Bulletin:

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 environment or favorable our genes? And finally for all of us, the most important question: How can insights into longevity be used to fight the diseases and disabilities associated with old age to improve the odds that aging will be healthy, active, and independent.

Although chronological aging is inevitable, unlocking the secrets to "biological" aging is perhaps the ultimate scientific quest. Understanding the way cells age, as well as 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. Eighty-eight percent of those over 65 years of age have at least one chronic health condition[1]. Health-damaging behaviors, such as 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[2].

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

Theories abound regarding the biological causes of human aging. They fall primarily 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[3]. 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.

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. These regulators also control the dynamic balance between damage and repair, between energy production and decline, and even cell lifespan.

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.

Accumulation of Advanced Glycation End Products (AGE)
With age, our proteins, DNA, and other structural molecules develop damaging cross-links to one another. The accumulation of these cross-link-damaged proteins is tied to the debilitating effects of aging. When cross-linking occurs through a process called glycation, glucose molecules react with proteins in the body to form advanced glycation end products, or AGE, which
can form permanent, disabling cross-links that may contribute to cellular aging changes, especially in diabetics.

Replicative Senescence and Telomeres
Many human cells are known to have a finite capacity of cell divisions before they can no longer divide, a phenomenon 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.

Neuroendocrine Dysfunction
The neuroendocrine system refers to the complex connections between the brain, nervous system, and endocrine glands that release their hormones into circulation. As hormone production declines, neuroendocrine dysfunction 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 in 2007 alone[4]. 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 lifespan. Polyphenols, natural phytonutrients found in 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[5].

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 impacts 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[6].

Genetics and Calorie Restriction
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 study confirms that resveratrol may mimic, in mice, some of the effects of dietary or calorie restriction[7].

Mitochondrial Biogenesis and Aging
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[8].

AGE 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[9].

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 formation. This research suggests that consumption of specific grape polyphenols may have some benefit in influencing the progression of diabetic conditions[10].

Hormones and Aging
While many women with menopausal symptoms are helped by hormone therapy during and after menopause, some are placed at higher risk for certain diseases. For example, growth hormone appears to play a role in body composition and muscle and bone strength, but for now, there is no convincing evidence that it can improve the health of those who don't suffer a deficiency. DHEA production declines with age but it's unclear if this affects the aging process, and DHEA supplementation has been linked to liver damage in laboratory research[11]. The role of testosterone supplementation is under investigation for preventing frailty, but it remains unclear if supplementation of this hormone has any true benefit.

Exercise and Aging
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 with those in a more sedentary control group[12]. Elite athletes maintain a high level of fitness throughout their lifespan, but even the performance of elite marathon runners and weightlifters 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[13].

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. Adopting the following healthy behaviors will promote better living and a healthy anti-aging lifestyle.

- **Eat a Balanced Diet** low in saturated fats and rich in fruits and vegetables to have a positive impact on health conditions commonly seen in advancing age.
- **Maintain a Healthy Weight** to reduce the risk for the diseases of aging.
- **Engage in Regular Exercise,** including endurance and weight-bearing exercises.
- Increase intakes of **Vitamin D** 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 and cellular aging.
- Consider bioactive natural 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 that supports cellular function and longevity.
- **Quit smoking.** It's the most effective approach to reducing death and disease.

Finally, stress reduction, sufficient rest and sleep, and regular oral, vision, and hearing care are also effective tools to support a healthy anti-aging lifestyle.

"The aging of the population—in past decades and in the foreseeable future—presents both a challenge and an opportunity."

Dr. Richard J. Hodes, Director, National Institute on Aging (NIA), Director's Page, NIA website, February 2008.

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