Sylvia R. Karasu M.D.
The Gravity of Weight

AGING

The Intricate Choreography of Aging Gracefully

Part I: A search to prevent the mental and physical withering of old age.

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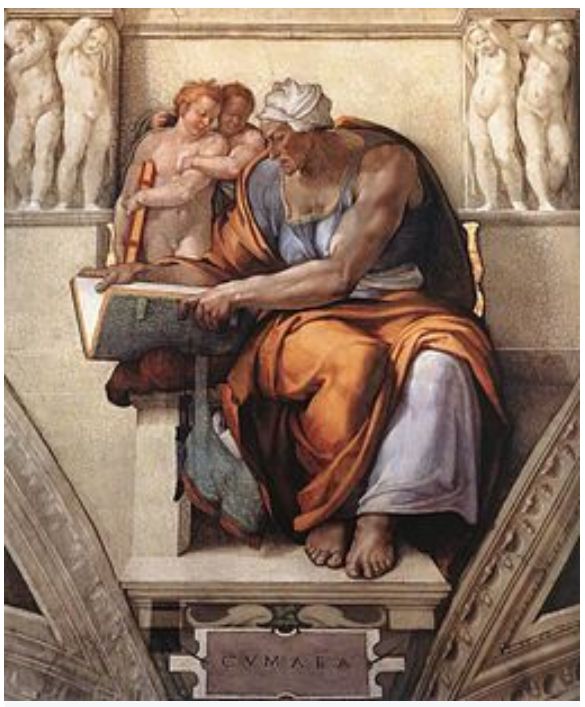
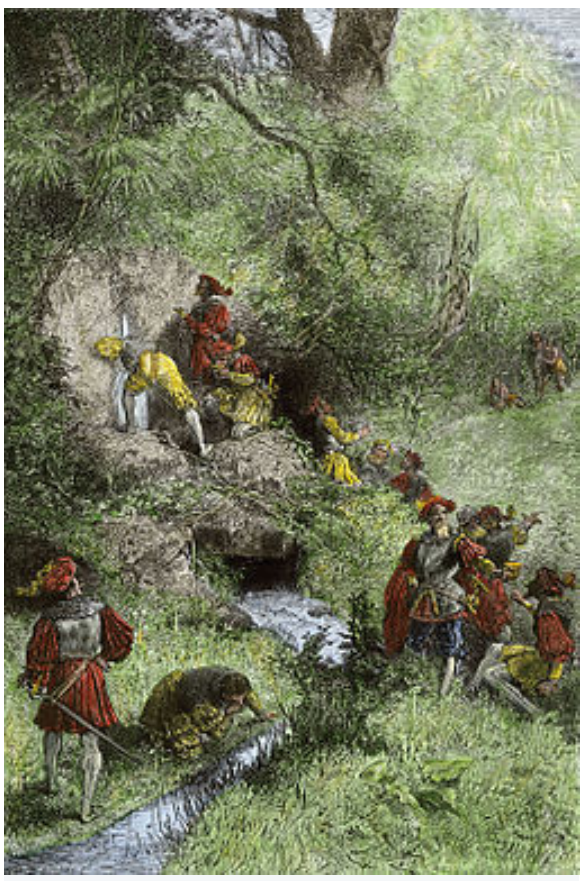


Painting of the Cumaean Sibyl on the ceiling of the Sistine Chapel, 1511, by Michelango. In the Virgil's Fourth Epilogue (sometimes called the "Messianic Epilogue,") the Cumaean Sybil offers a prophesy of the birth of a child that some Christians believe foretold of Jesus' birth. Source: Wikimedia Commons/Public Domain

The Cumaean Sibyl, a "mere mortal" but prophetess to Apollo, was 700 years old when she escorted Aeneas to the Underworld to visit his dead father Anchises. She would live to be 1000. She explains that she had gathered up a handful of sand and requested from the god Phoebus, whom she had rejected, to live as many years as the grains. “But I forgot to ask that I stay young through all that span.”(Ovid, *Metamorphoses*, Book XIV) Instead, her long life leaves her “shriveled, worn away by age.” There are many images of the Cumaean Sibyl in art, with perhaps the most famous preserved by Michelangelo on the ceiling of the Sistine Chapel.

Likewise, the goddess Aurora fell in love with Tithonus, the son of a king of Troy, and asked Zeus to grant Tithonus immortality. Aurora, as well, forgot to ask for eternal youth for her husband. (*Britannica* online) Tithonus did gain immortality, though, in the poem by Alfred, Lord Tennyson, “Me only cruel immortality/ Consumes: I wither slowly in thine arms… Immortal age beside immortal youth… cold my wrinkled feet.” (Poetryfoundation.org)

Throughout human history, there are countless references in art and literature to those who seek immortality. For example, *The Epic of Gilgamesh*, written by a Babylonian scribe more than 1000 years before Christ, tells of Gilgamesh’s quest for eternal life from Utanapishtim, the only human to survive the Great Flood. Alas, Gilgamesh fails the obligatory tests, and he, too, gains eternal life only through his epic story that has survived for centuries. (*Ancient History Encyclopedia* online.)

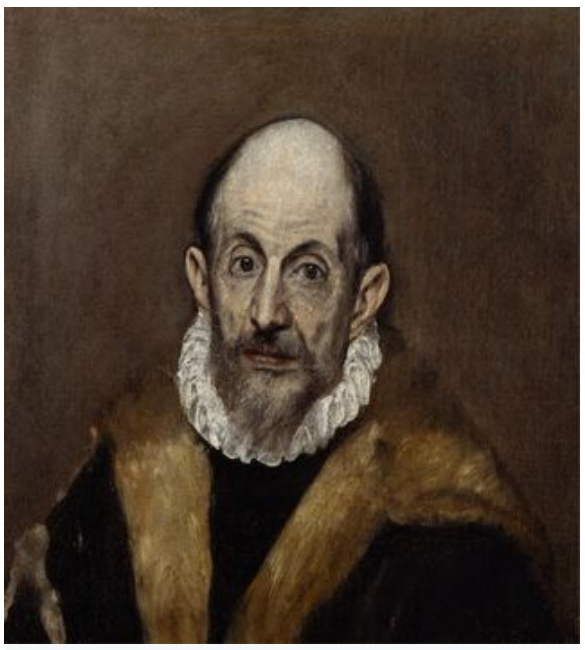


19th-century depiction by an unknown German artist of Ponce de Leon's search for the "Fountain of Youth" in Florida. This story of the Spanish explorer is apocryphal and not accepted as fact by historians.
Source: Wikimedia Commons/Public Domain

Further, there is the apocryphal story, also preserved in art, of 16th-century Spanish explorer Ponce de León: reportedly, he unsuccessfully sought the "Fountain of Youth," whose waters rejuvenated those who drank from it, in the Florida area. (*Britannica Online Encyclopedia*) And even Dorian Gray, of Oscar Wilde fame, makes a Faustian bargain to remain eternally youthful: only his portrait, immortalized by Ivan Albright at the Art Institute of Chicago, cruelly ages. (See my previous blog for a discussion of Dorian and Albright’s picture)

What is aging? For some researchers, it is a result of an imbalance between pro-inflammation and anti-inflammation, resulting in a low-grade pro-inflammatory state. (Li et al, *Biofactors,* 2018) For others, it is a “breakdown of biological robustness”—a process of systemic, progressive, functional decline.” (Imai, *Nature Partner Journals, Systems Biology and Applications,* 2016.) “Biological robustness” has been defined as a maintenance of bodily *functions* against internal and external perturbations” and is a more general concept to

be differentiated from homeostasis, which involves maintenance of steady system *states.* (Kitano, *Molecular Systems Biology*, 2007) Some of the hallmarks of aging include mitochondrial dysfunction, epigenetic alterations, and genomic instability. (Imai, 2016) Investigators believe that a deterioration in mitochondrial functioning and the resultant cellular energy deficit "have emerged as critical factors" in aging and its diseases. (Verdin, *Science*, 2015) Researchers, though, are far from understanding the structure and dynamics of aging, including which organs play key roles in determining the human lifespan, as well as what determines the rate at which our biological robustness breaks down. (Imai, 2016)



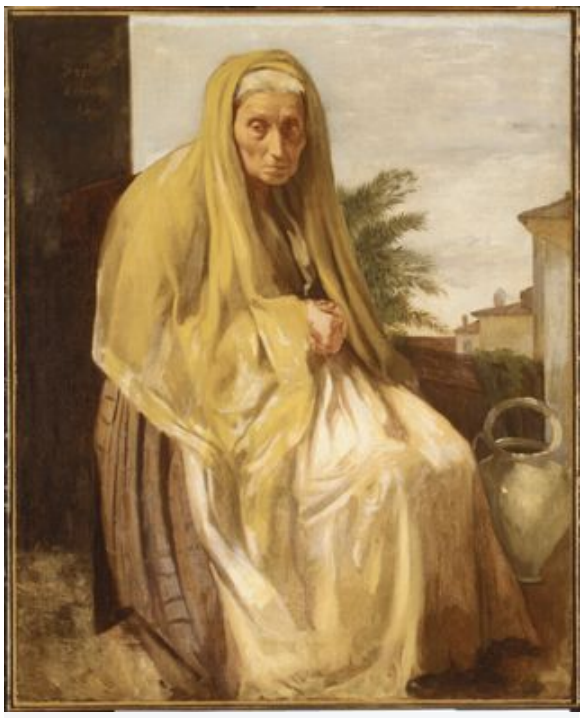
Portrait of an Old Man by El Greco, 1595-1600. Source: Public Domain, Metropolitan Museum of Art, NYC. Credit: Purchase, Joseph Pulitzer Bequest, 1924.

Nicotinamide adenine dinuceotide (NAD+) was originally discovered in experiments with yeast and fermentation in 1906. (Verdin, 2015; Yoshima et al, *Cell Metabolism*, 2018) For about a century, NAD+ had been known as a "fundamental housekeeping molecule" involving electron transfer in reduction-oxidation (redox) metabolic reactions. (Kane and Sinclair, *Circulation Research*, 2018) NAD+ is involved in regulating energy metabolism, DNA damage repair, gene expression, and the stress response through its interaction with various enzymes. (Okabe et al, *Journal of Biomedical Science,* 2019) There is a kind of "critical choreography" between coenzymes and proteins, including the group of sirtuins, a family of proteins involved in metabolic regulation with which NAD+ is intricately involved. (Dellinger et al *Nature Partner Journals: Aging and Mechanisms of Disease*, 2017)

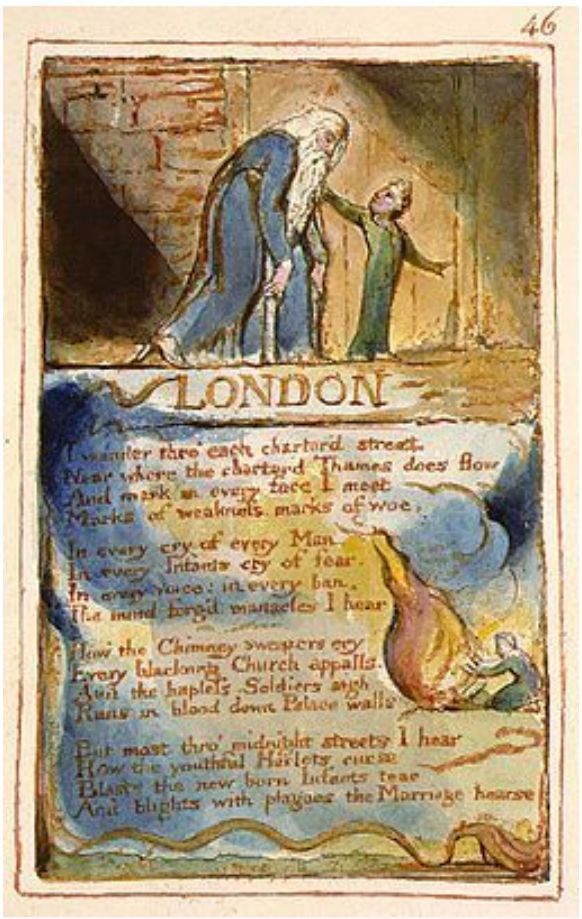
What researchers have found is that levels of NAD+ naturally decline as we age and alterations in NAD+ can be found associated with all age-related diseases such as diabetes, cancer, and even neurodegenerative diseases. (Katsyuba et al, *Nature Metabolism,* 2020) When NAD+ levels decline, there is a compromised communication between the nucleus and mitochondria, and this leads to decreased levels of sirtuin activity as well. Sirtuins "have evolved" to respond to how much NAD+ is available. (Imai and Guarente, *Nature Partner Journals*, *Aging and Mechanisms of Disease,* 2016)

NAD+ has undergone a veritable "conceptual revolution" from being seen as a "simple metabolic co-factor" to a "pivotal co-substrate" for proteins that regulate metabolism and longevity." (Katsyuba et al, 2020) Increasing NAD+ is now also seen as a means to create *healthspan,* i.e., not necessarily increasing the human lifespan but living healthier, disease-free lives as we age. (Verdin, 2015) Interest in NAD+ and the means of replacing these declining levels have led to a "genuine scientific renaissance" in the media as well, (Katsyuba et al, 2020) including a feature in *Time Magazine*, "Is an Anti-Aging Pill on the Horizon?" (Sifferlin, *Time,* 2/15/2018)

NAD+ can be synthesized *de novo* from the amino acid tryptophan but this does not occur on all tissues and requires a so-called *salvage* pathway from precursor molecules. (Katsyuba and Auwerx, *The EMBO Journal, 2017)* Since NAD+ is not permeable to the plasma membrane, researchers must use NAD+ precursors, including nicotinic acid, tryptophan, nicotinamide mononucleotide (NMN), and most commonly, nicotinamide riboside (NR.) (Okabe et al, 2019) Vitamin B_3 (niacin, i.e., nicotinic acid and nicotinamide) can act as a NAD+ precursor but nicotinic acid taken orally is often associated with the uncomfortable symptom of flushing and nicotinamide apparently does not "reliably activate" the sirtuins even though it raises NAD+ levels. (Martens et al, *Nature Communications*, 2018) That there are different pathways for NAD+ production raises the question of the importance of each pathway and which one can lead to the highest level of NAD+ production. (Katsyuba and Auwerx, 2017) NAD+ intermediates can be found naturally in cow's milk and unprocessed foods, (Trammell et al, *Nature Communications*, 2016) including vegetables (e.g. broccoli and cucumber), fruits, and beef. (Okabe et al, 2019; Yoshina et al, *Cell Metabolism,* 2018.)

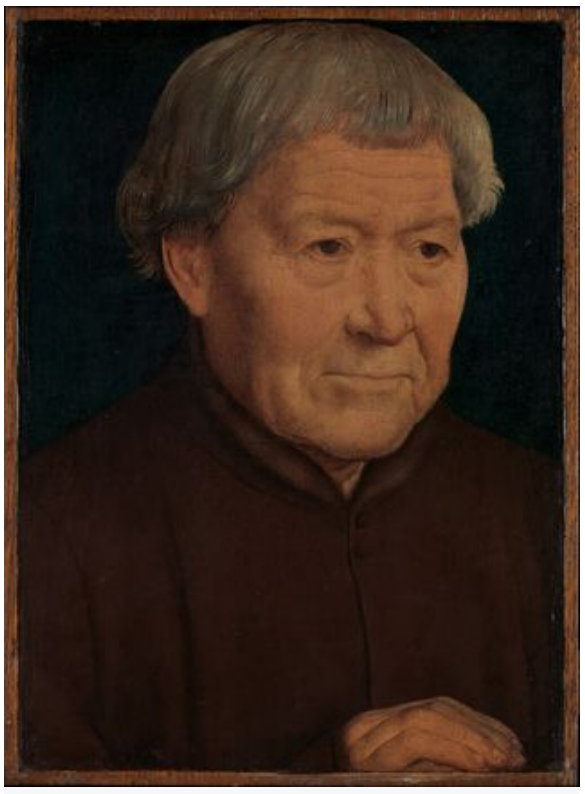


"The Old Italian Woman" by Edgar Degas, 1857. Source: Metropolitan Museum of Art, NYC. Public Domain. Credit: Bequest of Charles Goldman, 1966.



William Blake's "Songs of Innocence and of Experience," "London," 1794, Fitzwilliam Museum, The William Blake Archive.
Source: Wikimedia Commons/Public Domain

Further, NAD+ levels can increase in response to conditions considered "low energy load," such as fasting, caloric restriction, and exercise. (Verdin, 2015) Caloric restriction, without malnutrition, has been shown to be an "effective nutritional intervention," particularly in many animal species, to counteract aging and even prevent metabolic and cardiovascular diseases. (Li et al, 2018) Long-term studies in humans are ongoing, but investigators still do not know what level of caloric restriction is required, at what age is it best to begin, and how long it must be followed for actual health benefits. Since caloric restriction, though, is so difficult for most people to maintain over extended periods of time, researchers have searched for alternatives, including increasing NAD+ levels, that can mimic its effects. (Martens et al, 2018)



Portrait of an Old Man, circa, 1475, by Hans Memling.
Source: Metropolitan Museum of Art, NYC. Credit: Bequest of Benjamin Altman, 1913.

There is so much, though, that is still unknown about NAD+ and the sirtuins, including possible different effects on men and women, particularly in regard to cardiovascular and metabolic diseases. Further, researchers still know little about their cellular transport and even the role diet may have. (Kane and Sinclair, 2018) Not only dosing, but the optimal timing of dosing for an NAD+ precursor is an issue because NAD+ levels fluctuate with circadian rhythms. (Verdin, 2015) Most studies, to date, have been pre-clinical research in mice but that is changing, and there are now many human studies registered with ClinicalTrials.gov. In Part II of this discussion, I will focus on some of the clinical studies, as well as discuss pterostilbene, an antioxidant found in blueberries and given together with an NAD+ precursor.

About the Author

Sylvia R. Karasu, M.D., is a clinical professor of psychiatry at Weill Cornell Medical College and the senior author of *The Gravity of Weight.*

In Print: *The Gravity of Weight: A Clinical Guide to Weight Loss and Maintenance*

Online: my own website