



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

"A Privileged Way of Knowing:" Science and Aging Gracefully

Part 2: Attempts to increase our health span and ward off the effects of age.

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"The Assassination of Cicero," 15th century, by an unknown artist. Cicero, the Roman statesman and orator, was only about 63 years old when he was killed on the order of his political rivals. He never was able to experience the joys of advanced old age he chronicles in his essay, written within the year before his death.
Source: Wikimedia Commons/Public Domain

Marcus Tullius Cicero, the Roman statesman and perhaps the greatest orator of his era, wrote his classic work *de Senectute*, *On Old Age*, when he was about 63 years old. Alas, Cicero never got to experience the glorious benefits of advanced old age that he chronicles: within the year, he was assassinated—beheaded—on the order of his political rivals.

Cicero had even successfully defended in court the man, merely attempting to curry favor with those in power, who murders him. (Peck, editor, *Harper's Dictionary of Classical Literature and Antiquities*, pp. 339-345, 1963) And we think our American politicians behave egregiously!

In *de Senectute*, though, Cicero makes an heroic effort to persuade his audience that elegance and authority come with old age. Most people, though, will find Cicero's essay unconvincing and prefer to avoid the almost inevitable frailties and deterioration that old age

brings. Both the mythological figures of the Cumaean Sibyl, the prophetess of Apollo, and Tithonus, son of a king of Troy, were granted long life by the gods but without remaining young, they bemoaned their fate of a withering and infirm old age and even preferred a death that was no longer available to them.

In Part I, I wrote about the declining levels of NAD⁺—nicotinamide adenine dinucleotide—that occur naturally with age and the possibility of replacing these levels by administering precursors such as nicotinamide riboside (NR). The pharmacokinetics within the human body, though, remain poorly understood, including how these precursors are metabolized in the liver and blood after oral administration. (Yoshino et al, *Cell Metabolism*, 2018) Further, there is even a report that increasing NAD⁺ levels could foster the growth of tumors since drugs that deplete NAD⁺ levels are in development as a cancer treatment. (Yoshino et al, 2018)



"The Young Cicero Reading," painting, circa 1464, by Vincenzo Foppa. The Wallace Collection, London.
Source: Wikimedia Commons/Public Domain

Investigators emphasize that many people take these supplements outside of clinical trials and hence side effects may typically go unreported. "Although the therapeutic potential of boosting NAD⁺ levels is undeniable, it is time to pause and ponder the potential repercussions" related to the NAD⁺ replacement. (Katsyuba et al, *Nature Metabolism*, 2020.)

The first clinical trial of NAD⁺ supplementation in 12 healthy volunteers, administering different dosages on three separate days, occurred only in 2016 and demonstrated that NR did increase blood levels of NAD⁺. (Trammell et al, *Nature Communications*, 2016) There have been a few other short-term studies. Depending on the population studied, nicotinamide riboside (NR) did not lead to any serious adverse effects, "but did not result in any striking improvements in any disease to date." (Katsyuba et al, 2020) There is some suggestion that after 21



Self-Portrait, Rembrandt, 1660. Rembrandt was only age 54 when he painted this portrait, one of 40 self-portraits that survive. He was "unsparing in depicting the signs of aging in his own face." (Met Museum description.)

Source: Metropolitan Museum of Art, NYC/Public Domain. Credit: Bequest of Benjamin Altman, 1913.

days of supplementation, there were diminished levels of inflammatory cytokines as well as a trend to decrease blood pressure. Further, researchers caution that there needs to be better methods for accurate measurements of NAD⁺ levels. (Katsyuba et al, 2020)

Substances that have also gained the interest of both scientists and the media are the stilbenes—natural phytochemicals (400 different ones have been identified) that are found in many plants, fruits, and vegetables. (Pan et al, *Biofactors*, 2018) These are anti-oxidants, i.e., reduce oxidative stress; they are protective against free radicals (Li et al, *Biofactors*, 2018) and are similar to resveratrol, the substance found in red wine and grapes. Because of their slightly different chemical structure, these stilbenes have better cellular uptake, membrane permeability, bioavailability, and a longer half-life than resveratrol. (Riche et al, *Journal of Toxicology*, 2013; Pan et al, 2018) One of them, pterostilbene, is a potent anti-inflammatory and is the natural compound found in blueberries.

In recent years, blueberries have been labeled a “superfruit,” but this is a “virtually meaningless term in scientific research,” clarifies James Hamblin, MD (*The Atlantic*, November 15, 2017). Their popularity has more to do with savvy marketing than any super property. There have even been conferences worthy of the American Civil War, with titles like “The Blue Versus the Gray” in which researchers tout the potential benefits of blueberries for healthy aging. (Ingram, *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 2019)

Studies, though, are difficult to conduct and have been subject to criticism. For example, Allison and colleagues (Vorland et al, *Letter to the Editor, PsyArXiv Preprints*, 2020), after conducting a thorough statistical analysis, were not able to replicate findings presented in the systematic review by Hein et al (*The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 2019) on the effects of blueberries on cognition. Likewise, Brydges and Gaeta, in a *Letter to the Editor*, found errors in another systematic review on blueberries and concluded, “Based on the current research, researchers should avoid drawing definite conclusions regarding the effects of blueberries on cognitive performance or mood.” (*Brain, Behavior, and Immunity*, 2019.)

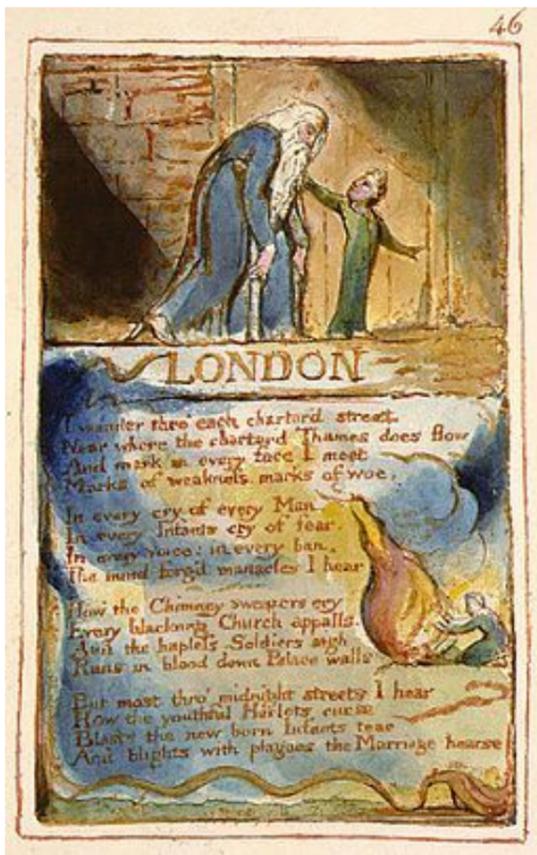
Nevertheless, pterostilbene (PT) itself has been subject to study, particularly to assess its safety. (Riche et al, 2013; Riche et al, *Evidence-Based Complementary and Alternative Medicine*, 2014) These researchers emphasize that since it is classified as *Generally Recognized as Safe (GRAS)*, it remains exempt from any premarket FDA regulations. They found, in their randomized controlled study of 80 subjects, that PT reduces blood pressure (dose-dependent) but increases levels (unknown significance and cause), of LDL and total cholesterol. (Riche et al, 2014)

In another study, nicotinamide riboside (NR) was given with PT. The combination of the two was predicted to work synergistically. This was the first trial of a repeat dose in 120 healthy adults between 60 and 80 with this combination. There was a rise in total cholesterol and LDL but when subjects were stratified by BMI, increased levels were not considered significant and may have also been the result of the “vagaries of randomization” and the fact that LDL levels can vary by as much as 9%. (Dellinger et al *Nature Partner Journals: Aging and Mechanisms of Disease*, 2017) There are currently four trials sponsored by industry and registered with ClinicalTrials.gov in which researchers are using a combined pill of pterostilbene and nicotinamide riboside to study inflammatory markers; muscle metabolism and exercise; subjective well-being after falls in elderly patients; and changes in liver fat.

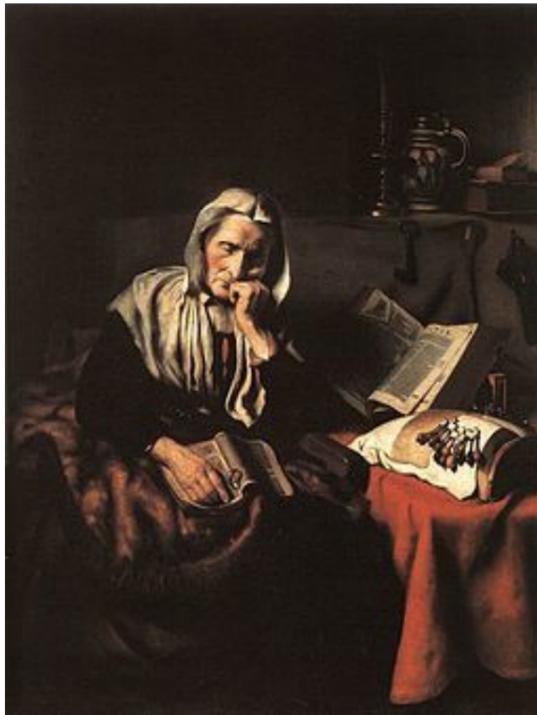


Gustave Caillebotte's "Fruit Displayed on a Stand," circa 1881. Museum of Fine Arts, Boston. Many studies of blueberries have been criticized. Labeling the blueberry as a "super fruit" reflects savvy marketing and is a "virtually meaningless term in scientific research."

Source: Wikimedia Commons/Public Domain



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



"Old Woman Dozing," by Nicolaes Maes, circa 1656, Royal Museums of Fine Arts of Belgium.
Source: Wikimedia Commons/Public Domain

ClinicalTrials.gov that are evaluating the effects of administering compounds to replace either nicotinamide adenine dinucleotide (NAD+) and/or the anti-oxidant pterostilbene. Because these substances are registered as Generally Regarded As Safe (GRAS), they are not subject to the rigorous testing and regulations of the FDA.

To date, most of the studies are in the recruitment phase or are still ongoing, and hence there are very few results that are published in peer-reviewed journals or even available for evaluation. Further, research is short-term (e.g., several weeks or months). We do not know the effects of these substances when taken chronically or even the most efficacious dose to recommend.

Fortunately, science, the “privileged way of knowing,” that involves gathering evidence and being willing to change our theories in light of new evidence, will enable us to evaluate this research.

This is the second part of a two-part blog on aging and NAD+. [Click here for the first post.](#)

Lee McIntyre writes that what is distinctive about science is not its subject or its method but its *attitude* toward empirical evidence and a willingness to change its theories on the basis of evidence (*The Scientific Attitude: Defending Science from Denial, Fraud, and Pseudoscience*, p. 7, 2019). For McIntyre, science is a “privileged way of knowing” (p. 205), and the scientific attitude “is more than an individual mindset; it is a shared ethos that is embraced by a community of scholars who are tasked with judging one another’s theories...” (p. 112)

The bottom line:
Replenishing naturally declining coenzyme levels or phytochemicals to stave off the mental and physical withering effects of old age makes clinical sense. Preclinical animal studies, particularly mouse models, provide strong evidence that metabolic and cardiovascular diseases can be ameliorated or even reversed, and analogously may increase our own human *healthspan*, i.e., not necessarily living longer, but living healthier and relatively disease-free as we age.

The transition from "bench to bedside," though, may not be so straightforward and requires gathering considerably more empirical evidence. There are currently many human studies registered with



"The Old Courtesan," by Auguste Rodin, ca. 1885, cast 1910. Rodin captures the withered and deteriorated body of old age.
Source: Metropolitan Museum of Art, NYC. Public Domain, Credit: Gift of Thomas F. Ryan, 1910.



Lucas Cranach, the Elder, "The Fountain of Youth," 1546. Gemaldegalerie, Berlin.
Source: Wikimedia Commons/Public Domain

About the Author



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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 Michelangelo. 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

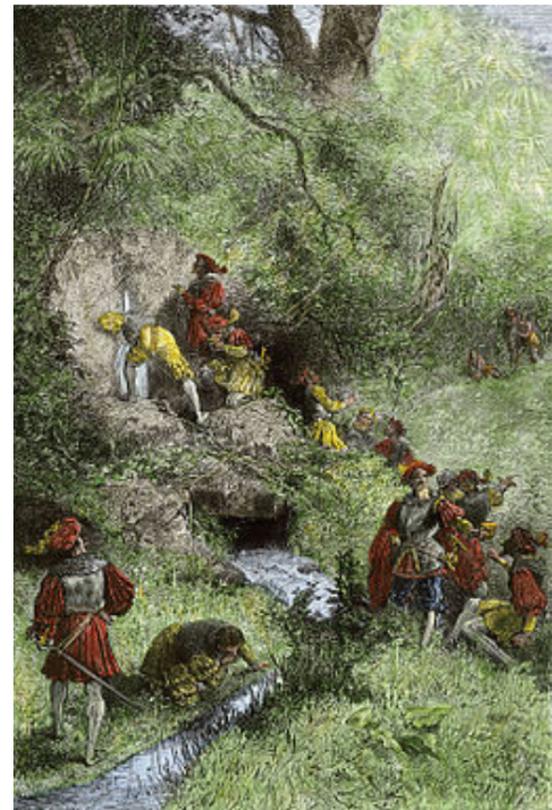
The Cumaean Sibyl, a "mere mortal" but prophetess to Apollo, was 700 years old when she escorted Aeneas to the Underworld to visit his dead father Anchises. She would live to be 1000. She explains that she had gathered up a handful of sand and requested from the god Phoebus, whom she had rejected, to 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.)

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



19th-century depiction by an unknown German artist of Ponce de León'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

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 dinucleotide (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)

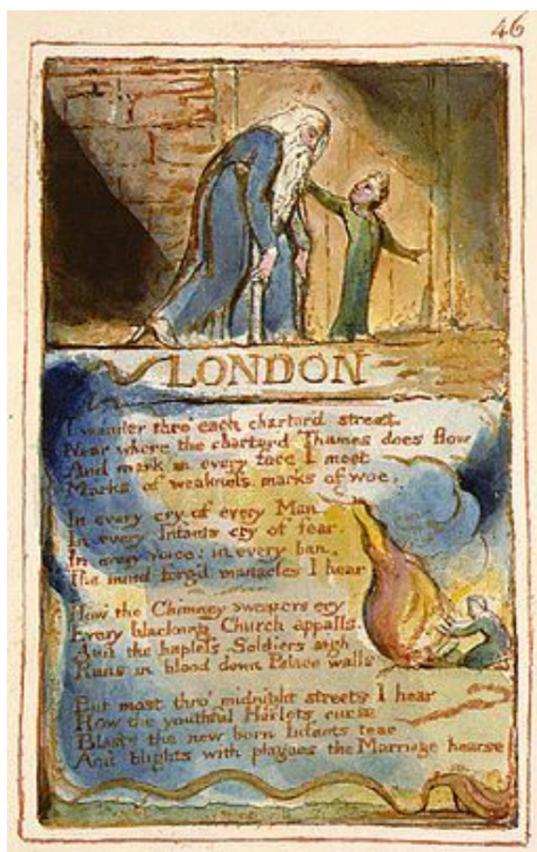
What researchers have found is that levels of NAD⁺ naturally decline as we age and alterations in NAD⁺ can be found associated with all age-related diseases such as diabetes, cancer, and even neurodegenerative diseases. (Katsyuba et al, *Nature Metabolism*, 2020) When NAD⁺ levels decline, there is a 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 B₃ (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

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.

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)

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,



Portrait of an Old Man, circa, 1475, by Hans Memling.

Source: Metropolitan Museum of Art, NYC. Credit: Bequest of Benjamin Altman, 1913.

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