NICOTINAMIDE

GOLDEN THREAD IN THE TAPESTRY OF LIFE

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I don't believe in aging. I believe in forever altering one's aspect to the sun.
- Virginia Woolf

"Mutant mice live longer."[1] That is the admirably plainspoken title of a recent paper by Dr. Leonard Guarente, the MIT biologist whose pioneering work has greatly expanded the most exciting new vista in aging research: the study of how certain genes may slow down the rate of aging in creatures from bacteria and fungi to mice and humans. In the article in question, Dr. Guarente discusses recent work by other researchers showing that mice with an induced mutation in a certain gene seem to live almost one-third longer than normal mice.[2] The mutation (an alteration in the mice's "aspect to the sun," one might say) prevents production of the protein molecule, called $p66^{shc}$, that the gene in question codes for. The absence of this protein enhances the organism's resistance to agents, notably free radicals, that cause oxidative damage to its cells. Thus, the mutant mice live longer.

This discovery adds support to the belief that oxidative damage to our cells is one of the principal mechanisms (but by no means the only one) of aging. In addition to illustrating that not all genetic mutations are harmful, **the discovery is especially significant for being the first demonstration that a simple genetic modification of the cellular response to oxidative damage can increase lifespan in a mammal.** Previously, this had been shown only in mutants of yeasts, nematode worms, and fruit flies. As humans, we would much rather see encouraging scientific results demonstrated in creatures such as, well, mice, that are pretty close to us on the evolutionary tree of life. (Overall, 85% of our gene sequences are identical to those of mice, and 86% of the gene sequences that code for diseases are identical.)

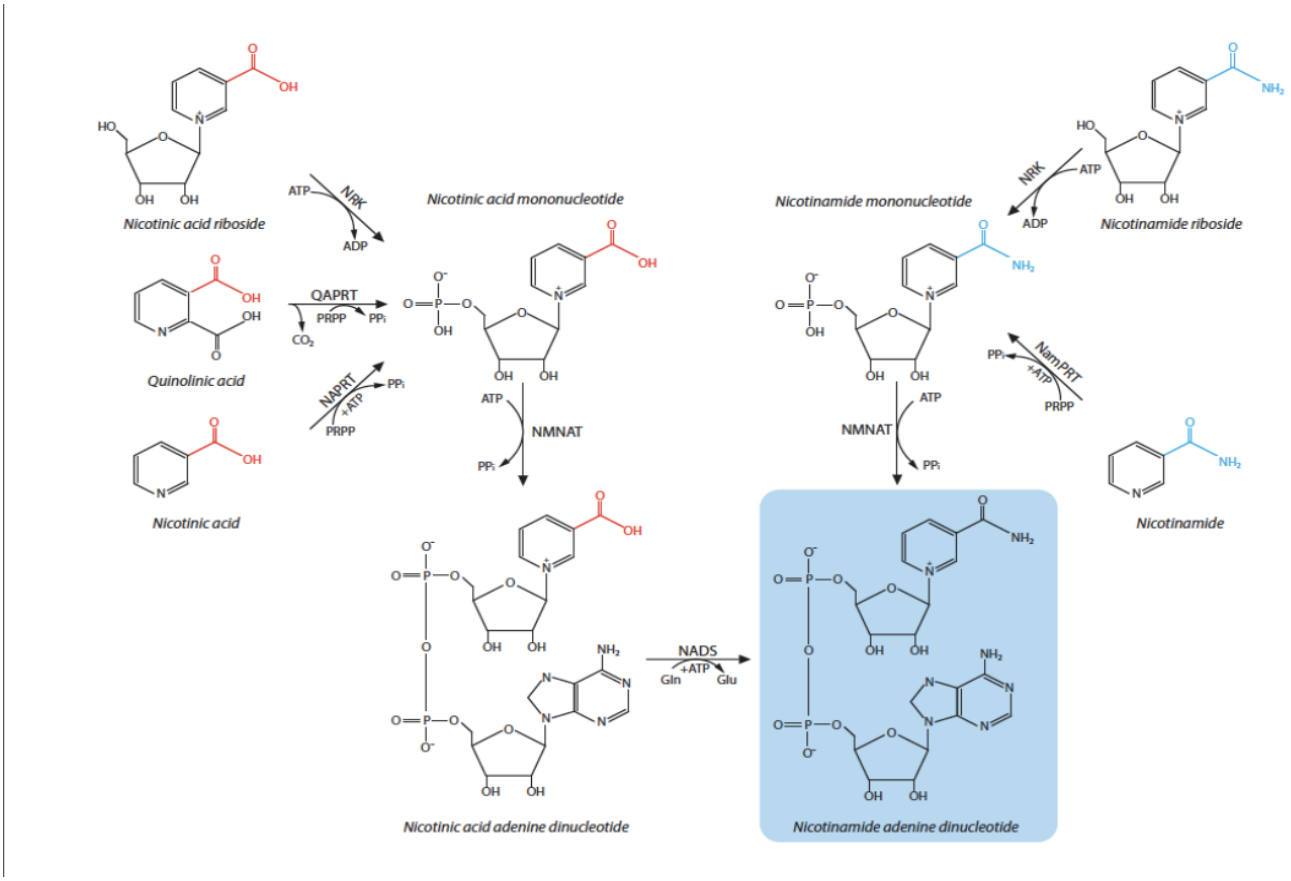
NAD - ONE OF LIFE'S GOLDEN THREADS

The study of the genetic basis of aging is still in its infancy, and the heady excitement of new discoveries being made in laboratories around the world is tempered by the considerable confusion about how to interpret them. It's a great time to be a molecular biologist with the spirit of adventure and a taste for controversy. Biochemistry and genetics are complicated subjects, and it can take the patience of a saint, as well as formidable scientific skills, to unravel the molecular threads that make up the exquisite tapestry of life.

It always helps, of course, when one particular thread in the tapestry appears again and again, like a leitmotif in a Wagner opera, to link seemingly disparate elements of the picture, thus helping to make it a bit clearer. It's especially helpful if such a thread appears not just in different parts of the picture of a given organism, but in those of many *different* organisms, from the simplest to the most complex. Together, they make up the Big Picture.

One such pervasive thread is a molecule called *nicotinamide adenine dinucleotide,* or NAD, which is closely associated, as a cofactor, with another thread, a protein called *Sir2p.* **NAD and Sir2p have been discovered, in experiments with yeasts, to play a key role in suppressing one of the aging mechanisms to which most living organisms are believed to be vulnerable.** The mechanism in question is the accumulation in our cells of bits of rogue DNA called *extrachromosomal rDNA circles,* or ERCs, the ultimate effect of which is to "choke" the cells to death. And when too many of our cells die, we die.

NAD



NAD IS VITAL FOR GENE SILENCING

The inhibition of this aging process is called *gene silencing* ("Sir" stands for "silent information regulator") because certain genes that are implicated in the process are "silenced," i.e., they are prevented from carrying out their normal function. (Not all gene silencing has to do with aging; other examples of this phenomenon, e.g., involve protecting the organism from foreign nucleic acids, such as those from viruses.)

The star performer in this biochemical drama of life and death, Sir2p, can play its role only in conjunction with NAD, without which it is as impotent as Samson after his run-in with Delilah. Indeed, researchers at the Johns Hopkins University School of Medicine have found that if a

gene called NPT1, which is important in the synthesis of NAD from nicotinamide, is removed, creating what is called an *npt1* null mutant, NAD levels in the cell drop sharply, and the Sir2p-induced gene-silencing process is severely curtailed.[3]

The authors of this study reported, "The fact that this significant drop in intracellular NAD^+ has only negligible effects on general cell growth and vigor in *npt1* mutants contrasts with striking and specific silencing defects. High levels of NAD^+ may be required to maintain silencing but not other aspects of cellular metabolism." Further confirmation of the role of NAD (NAD^+ is its ionized form) is given by the authors of a related paper, who state that "If Sir2 uses NAD^+ as a cofactor to modify histones or other proteins in a step that is required for silencing, as the results presented here suggest, then defects in NAD^+ biosynthesis resulting in changes in the intracellular levels of NAD^+ may be expected to affect the efficiency of silencing in yeast. . . . **These results suggest that the efficiency of silencing is extremely sensitive to a reduction in the intracellular pools of NAD^+."**[4]

NAD IS READILY OBTAINABLE FROM NIACINAMIDE

Exactly how Sir2p accomplishes gene silencing, and exactly how NAD helps it do this, are far from being well understood, and there is much speculation and controversy - most of it far too technical to be understandable, let alone interesting, to laypeople - based on the growing body of experimental evidence in this field. What matters to us are four things:

1. The critical importance of NAD in the gene-silencing mechanism is well established.

2. There are Sir2p-like proteins in a very wide variety of organisms, including humans, and they probably all perform essentially the same function.

3. There is reason to believe that an abundant supply of NAD in our cells is required for optimizing the gene-silencing process.

4. One of the chemical precursors of NAD is a well-known nutritional supplement: vitamin B3, more commonly called *niacin.*

Niacin should thus be exceptionally intriguing to those who wish to extend their lifespan through gene silencing. Whether niacin supplementation can actually do this is an open question and may remain so for a long time, but the theoretical possibility certainly exists. There are three related chemical compounds (inositol hexanicotinate, niacinamide, and niacinamide ascorbate) that have similar vitamin activity and that are also precursors of NAD, but that do *not* produce the notorious and annoying "niacin flush."

It's easy to get confused regarding the terminology of niacin and its relatives, so let's clear that up right now. Niacin is a synonym for nicotinic acid. When nicotinic acid, or niacin, is chemically modified by the addition of an amide group, it becomes nicotinic acid amide, or

niacinamide. And a synonym for that is *nicotinamide,* which is a part of the NAD molecule. There is an unnerving suggestion here of nicotine, an extremely poisonous compound (pure nicotine is a colorless liquid that looks like water but is readily absorbed by the skin; one drop of it will kill you). The similarity in names is not coincidental. Although nicotinic acid (essential for life) and nicotine (pure death) are different compounds, the former can be obtained by the chemical oxidation of the latter, and that is how it got its name. "Niacin" sounds much nicer.

(By the way, if you're a smoker, *please quit now,* because smoking can counteract many of the benefits of supplements. Smoking is among the worst things you can do if you're truly interested in life extension or life enhancement.)

NICOTINAMIDE IS A BETTER SOURCE OF NAD THAN NIACIN

Quite apart from its gentler, "flushless" quality, there is another reason to prefer nicotinamide (niacinamide) over niacin when it comes to gene silencing: it is a better source of NAD. This is not surprising, considering that it is one step closer to NAD in the chemical sequence niacin → nicotinamide → NAD. One study showed that the amount of NAD produced from nicotinamide was twice as great as that produced from niacin under physiological conditions.[5] The conversion process is enhanced by the presence of inorganic phosphate, but only for nicotinamide.

NADH DOES NOT PROMOTE GENE SILENCING

Closely related to NAD is its chemically reduced form, NADH, which is popular as a nutritional supplement because of its possible role in enhancing brain and body functions in Alzheimer's disease, Parkinson's disease, and chronic fatigue syndrome. NADH, however, is ineffective in promoting gene silencing by Sir2p, as NAD does.[6] In biochemical systems, a minor alteration in the molecular structure of one component can make a major difference in its biological activity. (There are, on the other hand, examples where even substantial alterations have relatively little effect; it all depends on the specifics of the molecular structures involved and the ways in which they interact with other molecules.)

NAD IS NEEDED FOR HEALTHY DNA, AND MORE

As should be obvious by now, niacin is beneficial not just for its actions as a vitamin (it prevents the disease called pellagra, among other things), but also indirectly for being a precursor to nicotinamide and, ultimately, NAD. Our health depends, in part, on having adequate amounts of NAD, which plays a profoundly important role in many aspects of cell function, such as the Krebs cycle for energy generation.

NAD also contributes to the molecular repair of nicks and breaks in the DNA of our chromosomes, the cumulative effect of which is always deleterious. A *deficiency* of NAD, therefore, compromises our ability to maintain good genetic health and is expected to act

synergistically with deficiencies of folic acid (one of the B vitamins) and antioxidants in causing DNA damage and cancer.[7] Conversely, adequate amounts of NAD have been shown to inhibit induction of cell proliferation.[8]

As a bonus, nicotinamide has been found to be beneficial in osteoarthritis.

Furthermore, the NAD precursors nicotinic acid and nicotinamide (aka niacin and niacinamide) have been shown to protect cells from *apoptosis,* a kind of programmed cell death (sometimes called cell suicide) that can be induced by cytotoxic substances such as bile salts.[9] The authors of this study, from the University of Arizona, observe that, "Since increased oxidative damage, DNA damage, and apoptosis are associated with numerous disorders, such as AIDS, inflammatory diseases, dermatologic diseases, cardiovascular disease, neurodegenerative diseases, aging, and cancer, NAD^+ precursors may prove useful as chemopreventive and therapeutic agents. . . . **we hypothesize that nicotinic acid and nicotinamide may be protective as dietary supplements for such conditions by increasing protective defenses against these deleterious effects."**

NICOTINAMIDE HELPS IN DIABETES AND OSTEOARTHRITIS

There are more good reasons to take nicotinamide. In a study of 56 recently diagnosed, insulin-dependent diabetic patients, 25 mg per kg of nicotinamide (2.0 g for a 175-lb individual) or a placebo was given over 12 months. The results showed that nicotinamide added to insulin in these patients can help prevent insulin-caused beta-cell destruction.[10] Researchers currently believe that nicotinamide may be able to help prevent insulin-dependent diabetes in susceptible individuals[11] (at least one trial is currently underway). This has been shown to be true in mice.[12] Since the byproducts of diabetes help accelerate the aging process,[13] it might be a good idea to take nicotinamide supplements as a preventive.

As a bonus, nicotinamide has been found to be beneficial in treating osteoarthritis. A recent pilot study found nicotinamide to produce a 29% improvement in "global arthritis impact." The erythrocyte sedimentation rate (the creation of red-blood-cell waste material) decreased by 22%, and joint mobility improved by 4.5 degrees, vs. controls.[14] Nicotinamide also reduced inflammation and allowed for a reduction in standard anti-inflammatory medications.

NAD OFFERS HOPE AS THE FIRST GENE SUPPLEMENT

In a paper published in 1996 entitled, "Do Changes in Chromosomes Cause Aging?," Dr. Guarente discussed the two major general models of aging: the *accumulated damage* model (such as oxidative damage from free radicals, as well as plain old wear and tear on bodily structures) and the *genetic program* model, in which our genes ultimately do us in via

mechanisms that we were only then beginning to understand.[15] He points out that these two models are not mutually exclusive, because it is possible that accumulated damage represents the timing mechanism that triggers a genetic program of aging.

In reference to the genetic program model, Dr. Guarente discussed four distinct molecular mechanisms for aging that centered on the possibility of chromosomal changes as the primary cause of aging. One of these was the loss of gene silencing, a process that is now much better understood than it was then, thanks in part to Dr. Guarente's own research.

He concluded by saying, "It is clearly too early to know with certainty what molecular events cause aging. An exciting possibility based on recent findings is that changes in chromosomal structure or function are a key determinant of aging. The methodology providing this new edge in aging research is the identification of specific genes that control the rate of aging in *S. cerevisiae* [brewer's yeast], *C. elegans* [a flatworm], and humans. It would perhaps be appropriate that chromosomes, which orchestrate the genesis, development, and maturation of organisms, also direct the final chapter in the life cycle."

If it is true, as now seems increasingly likely, that our chromosomes play a central role in the aging process, then it is probably wise to give them the nutrients, such as NAD, they seem to require for optimal functioning. It offers some hope that perhaps, at long last, we can stop complaining about our genes and do something about them.

Speaking of hope: In the mutant-mouse paper cited at the beginning of this article, Dr. Guarente concludes by saying, "We may be at a watershed in the study of aging. . . . We should . . . look forward to a growing research area nurtured by, if not the fountain of youth, more than a trickle of hope."