

## REPORT

### The Youth Restoring Benefits Of NAD+

By Scott Rahway

Since the year 2001, **Life Extension**<sup>®</sup> has been seeking a way to reverse a mechanism of aging that may not be adequately addressed by the healthy lifestyle choices most members currently follow.

Normal aging is accompanied by a noticeable increase in **fatigue** and **loss of motivation**. The tiredness we outwardly feel reflects inward impairment of cellular functions critical to sustaining life.

**NAD+** is the term used in the scientific literature to describe a cellular compound called *nicotinamide adenine dinucleotide*.

**NAD+** is found in every cell in the body and is essential to life.<sup>1,2</sup> **NAD+** enables the transfer of energy from the foods we eat to vital cell functions. It is also required to “turn off” genes that accelerate degenerative aging processes.<sup>3,4</sup>

As **NAD+** levels decline, mitochondrial function is impaired, resulting in fewer mitochondria surviving.<sup>3,5</sup> This vicious cycle of mitochondrial depletion results in many of the physical symptoms of aging.

The challenge we at **Life Extension** have faced over the past 13 years is finding an efficient way for aging humans to affordably boost their **NAD+** cellular levels.

In **2001**, one of our researchers developed an effective **NAD+** boosting sublingual lozenge, but it only maintained stability for a short time period. As you’ll read in this article, an effective **NAD+** cell boosting technology has finally become available.

Prominent universities have been investigating **NAD+** as a potential therapy for age-related degenerative disease.<sup>6</sup> Compelling research shows that **NAD+** has a unique ability to protect tissues, induce DNA repair, and increase life span.<sup>2,7,8</sup>

It has long been known that **NAD+** plays an important role in transferring energy released from glucose and fatty acids to the mitochondria so that it can be converted into cellular energy.<sup>2,9</sup> Without sufficient **NAD+**, energy transfer in the cells breaks down, resulting in age-accelerating *mitochondrial dysfunction*.<sup>5,10,11</sup>

**NAD+** is an essential cofactor of key *enzymes* responsible for longevity called *sirtuins*.<sup>5,12,13</sup> While **resveratrol** is well known for sirtuin activation, evidence indicates it does so *indirectly*,<sup>14,15</sup> whereas **NAD+** *directly* activates sirtuins to regulate the genes of aging.<sup>2,16</sup>

Sirtuins, specifically **SIRT1** and **SIRT3**, are intimately related to longevity through their control of gene expression and require **NAD+** for their activity.<sup>2,3,10,17-19</sup>

Research into the sirtuins continues to yield substantial information on how to control aging. By activating these sirtuins, we’re able to gain control over one of our body’s anti-aging “switches.” SIRT enzymes “turn off” certain genes that promote aging, such as those involved in inflammation,<sup>20,21</sup> in fat synthesis and storage,<sup>22,23</sup> and in blood sugar management.<sup>3,22,23</sup>

**SIRT enzymes** are activated by **calorie restriction**, the proven means of reliably extending life span in all organisms.<sup>2,24</sup> The way **calorie restriction** activates anti-aging **sirtuins** is by increasing cellular **NAD+**.<sup>2,25,26</sup>

### Consequences Of Falling NAD+ Levels

**NAD+** is found in every single cell in the body,<sup>1</sup> and is essential for efficient energy transfer from foods to tissues. **NAD+** is also required for turning off genes that accelerate aging.<sup>4</sup>

From a cellular energy standpoint, lower levels of **NAD+** reduce mitochondrial function, with fewer energy-rich ATP molecules being produced, and fewer mitochondria produced.<sup>5,11</sup> This vicious cycle results in many of the physical symptoms of aging.

The age-related decrease in **NAD+** causes defects in both energy- and gene-related functions to accumulate. These defects feed on one another to produce the disorders we typically identify as aging.<sup>10</sup> The consequences of a decline in **NAD+** levels and subsequent reduction in **SIRT 1** and **SIRT 3** enzymes are:

- **Neurodegeneration** in the brain,<sup>10,27,28</sup>
- **Vascular inflammation**, producing damage to blood vessels that can result in stroke or heart attack,<sup>27,29,30</sup>
- **Increased fat storage** in the liver, which can lead to nonalcoholic fatty liver disease (NAFLD),<sup>31-33</sup>
- **Increased fat production and deposition** in white adipose tissue, the primary fat storage form found in dangerous belly

fat,<sup>34,35</sup>

- **Insulin resistance**, preventing cells from appropriately removing glucose from blood, producing higher blood sugar levels and leading directly to metabolic syndrome,<sup>30,36,37</sup>
- **Fatigue, loss of muscle strength, and fatty infiltration of muscles**, resulting in reduced fatty acid oxidation (“burning”), thereby depriving muscles of their normal sources of energy.<sup>38,39</sup>

To avoid these degenerative processes, it is essential that steps be taken to optimize the amount of NAD<sup>+</sup> in our bodies.

By increasing intracellular **NAD<sup>+</sup>** levels, age-related **mitochondrial dysfunction** can be reversed.<sup>5</sup> One of the ways to accomplish this is by engaging in major **calorie restriction**, which has been proven to raise NAD<sup>+</sup> levels and in experimental organisms tested to date, to extend life span.<sup>5,25</sup> But most people find significant **calorie restriction** to be nearly impossible in practice.

Fortunately, a method has been developed to increase **NAD<sup>+</sup>** levels without having to alter dietary patterns, though **Life Extension** remains a strong advocate of **calorie restriction** for those able to consistently do it.

## A Natural NAD<sup>+</sup> Booster

Researchers have discovered a form of **vitamin B3** that converts in the body to **NAD<sup>+</sup>**.<sup>40,41</sup>

**Vitamin B3** is involved in over 400 enzymatic reactions throughout the body and is essential for production and management of cellular energy.<sup>42</sup> A new patented form of this vitamin called **nicotinamide riboside** has been found to increase **NAD<sup>+</sup>** levels and in the process, provide an extraordinary range of longevity benefits that promises to change how we combat aging.

Directly boosting NAD<sup>+</sup> with **nicotinamide riboside** presents a new and effective strategy for preventing the natural decline in cellular energy as we age by promoting youthful vitality.

Studies have shown that **nicotinamide riboside** switches “off” the genes of aging, extends life span, increases endurance, improves cognitive function, activates sirtuins, and enhances cellular energy.<sup>3,43</sup> These benefits add up to a system-wide slowing and reversal of certain aging processes. **Nicotinamide riboside** accomplishes this NAD<sup>+</sup> boosting effect without the irritating skin flushing and rash caused by the standard forms of vitamin B3.<sup>41</sup>

### WHAT YOU NEED TO KNOW

#### Systemic Anti-Aging Protection

- A major advance in “systemic anti-aging medicine” is now available for supplementation in humans.
- Nicotinamide riboside is a “next-generation” form of vitamin B3 that supports the vitamin’s functions throughout the body by boosting levels of a key metabolic cofactor called NAD<sup>+</sup>.
- NAD<sup>+</sup> is found in every single cell in the body, and is an absolute requirement for normal, efficient, and safe energy transfer from food to tissues.
- New discoveries show that NAD<sup>+</sup> is also essential for silencing genes for proteins that accelerate aging, such as those involved in inflammation, in fat synthesis and storage, and in blood sugar management.
- Supporting NAD<sup>+</sup> levels with nicotinamide riboside supplementation extends life span in laboratory organisms, while boosting energy, physical performance, and cognition in aging animals.
- To fight aging throughout your body by restoring youthful function of basic life-sustaining processes in every single cell, begin regular supplementation today with nicotinamide riboside.

## Initial Studies On Nicotinamide Riboside

In their investigations into the effects of **nicotinamide riboside** on life span, scientists used a strain of yeast known to have a relatively short average life span of about **8.3** generations.<sup>3,44</sup> When the yeast was treated with **nicotinamide riboside**, the average life span nearly doubled, to **16.1** generations. On this model of life span extension, ordinary vitamin B3 had no effect compared to the dramatic longevity benefit shown with **nicotinamide riboside**.<sup>3</sup>

**Nicotinamide riboside** is a dynamic compound that works through multiple mechanisms to promote life extension. Most dramatic are its effects on longevity and metabolism, as shown by recent laboratory studies.

One critical mechanism in oxygen-consuming organisms is mitochondrial function.<sup>45</sup> Mitochondria, the tiny, intracellular “furnaces” that power cellular processes, are sites of intense electrical and chemical activity.<sup>46,47</sup> They can readily “burn out,” contributing to the aging of tissues, and hence, of organs and entire organisms.

In a model commonly used to study life span modifications, the roundworm *C. elegans* could be made to survive as much as **16%** longer when supplemented with **nicotinamide riboside**. This life span extension was demonstrated to result from a

roughly **50%** increase in healthy mitochondrial oxygen consumption, a measure of mitochondrial efficiency.<sup>48</sup>

These benefits are what one would predict from **nicotinamide riboside** supplementation, which raises levels of the NAD+ needed to safely move electrons through the mitochondria.<sup>43</sup> We have long known that ineffective mitochondrial electron transport is an age-accelerating process.<sup>43,49,50</sup>

When pursuing additional lab studies, scientists found that supplementing mice with **nicotinamide riboside** reduced many dangerous factors of aging. The mice showed increased energy and improved insulin sensitivity, both factors indicating optimal vitality. In this study, scientists also demonstrated that nicotinamide riboside supplementation increased energy metabolism while protecting the animals against the metabolic abnormalities induced by a high-fat diet.<sup>43</sup> For the study, the mice were fed a high-fat diet with either no supplementation (control), or nicotinamide riboside for **12** or **16** weeks.

On a treadmill test, the supplemented animals fed a high-fat diet ran more than **33%** further than the control mice, demonstrating a dramatic increase in muscle endurance and performance.<sup>43</sup>

The supplemented mice also gained significantly less weight while on the high-fat diet compared to control animals. And in supplemented animals fed either the high-fat or a normal diet, insulin sensitivity (the ability to remove sugar efficiently from the blood) was greatly improved, compared with control animals.

Remarkably, these results were all attained *without any differences* in food intake or total physical activity between supplemented and control mice.<sup>43</sup> The supplemented animals lost weight, performed better at exercise, and managed their blood glucose better purely as a result of **nicotinamide riboside**-induced increases in calorie-burning (measured by increased oxygen consumption rates). This was confirmed by the observation that when the supplemented mice were exposed to prolonged cold conditions, they had significantly less body temperature loss compared to controls, the result of increased conversion of calories to heat.

Detailed analysis of the mice in this study revealed that supplementation with **nicotinamide riboside** had produced a significant increase in essential **NAD+** levels, resulting in the activation of the critical life span-extending enzymes **SIRT1** and **SIRT3**.<sup>43</sup> Supplementation with nicotinamide riboside also improved the numbers and function of **mitochondria**, the intracellular powerhouses that release energy from food; poor mitochondrial function is a known age-accelerator.

## Nicotinamide Riboside Protects Brain Cells

As cases of dementia and Alzheimer's reach epidemic proportions in the aging population, pharmaceutical companies are aggressively researching brain protective compounds.<sup>51,52</sup> **Nicotinamide riboside** with its ability to directly increase **NAD+** is providing promising brain benefits.

A recent lab study demonstrated the ability of nicotinamide riboside to protect brain cells in advanced age.<sup>9</sup> For the study, mice engineered to develop Alzheimer's disease were treated with **nicotinamide riboside** beginning at middle age (5 to 6 months) and lasting into old age (10 to 11 months).

The supplemented animals had significant improvements in their **cognitive function** in challenging laboratory tests of exploring new objects.<sup>9</sup> This improvement was shown to be associated with significantly reduced brain levels of *beta-amyloid plaques*, the abnormal protein that triggers much of the neuronal death and dysfunction in Alzheimer's disease. Intriguingly, supplementation had the added benefit of raising levels of the metabolic regulatory complex called **PGC-1-alpha**. Studies have shown that low levels of PGC-1-alpha have been associated with increased dangerous beta-amyloid deposition.<sup>9</sup>

The mechanisms by which these effects were achieved were found to include significant increases in brain levels of **NAD+** (the result of supplementation with nicotinamide riboside), and consequently activated enzymes involved in cellular energy production and energy release from glucose.<sup>9</sup>

In a similar study of neuroprotection, nicotinamide riboside was shown to delay the degeneration of axons, the "communication cables" of nerve cells that carry impulses over long distances.<sup>53,54</sup> When these communication cables deteriorate, tingling, weakness, numbness, and loss of motor function can occur as a result.<sup>55-57</sup> The mechanism behind this benefit was shown to be a significant **20-fold** increase in the enzyme that converts **nicotinamide riboside** to **NAD+**.<sup>54</sup>

Other studies in mammalian cells in culture demonstrate that nicotinamide riboside treatment increases NAD+ concentrations inside of cells by up to **2.7-fold**,<sup>58</sup> and that administering nicotinamide riboside can improve NAD+ related deficiencies in animal and yeast cells.<sup>24</sup>

**“Restoring NAD+ by supplementing NAD+ intermediates can dramatically ameliorate these age-associated functional defects, counteracting many diseases of aging, including neurodegenerative diseases. Thus, the combination of sirtuin activation and NAD+ intermediate supplementation may be an effective anti-aging intervention, providing hope to aging societies worldwide.”<sup>10</sup>**

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#### Summary

Researchers have discovered and patented a no-flush form of vitamin B3 that is revolutionizing the field of aging research.

Unlike earlier forms of this vitamin, **nicotinamide riboside** has been found to provide an extraordinary range of impressive **longevity benefits** that promise to change how science approaches the reduction of aging.

Studies have shown that **nicotinamide riboside** switches “off” the genes of aging, extends life span, increases endurance, improves cognitive function, activates sirtuins, and enhances cellular energy.

As we age, and our **NAD+** levels dramatically decline, we begin to experience fatigue and are more susceptible to neurodegeneration and cellular dysfunction. What makes the **nicotinamide riboside** form of vitamin B3 so unique is that once it is processed by the body it immediately converts into the powerful molecule **NAD+**.

**Nicotinamide riboside** accomplishes this **NAD+ boosting** effect without the irritating skin flushing and rash caused by the standard forms of vitamin B3.

If you feel increasingly lethargic or unmotivated as you age, you can probably blame your falling **NAD+** levels, which result in reduced cellular energy production.

Directly boosting NAD+ with **nicotinamide riboside** presents a new and effective strategy for preventing the natural decline in cellular energy as we age by promoting youthful vitality.

If you have any questions on the scientific content of this article, please call a **Life Extension**<sup>®</sup> Health Advisor at 1-866-864-3027.

#### HOW NAD+ DRIVES LONGEVITY-PROMOTING SIRT ENZYMES

SIRT enzymes regulate how genes are expressed from the DNA on our chromosomes in part by influencing chromosomal proteins called **histones**.<sup>59,60</sup> Research indicates SIRT enzymes have a “slot” capable of binding to one NAD+ molecule and one chemical acetyl (AC) group from the histone.<sup>61</sup> This binding triggers the SIRT enzyme to remove the acetyl group and bind the histone proteins more closely to their DNA strands, thereby regulating the expression of genes.<sup>4,17,31,62</sup> This is shown schematically below.

So, just as a coin in a parking meter slot adds time to the meter with each turn of the handle, a NAD+ molecule binding to a SIRT enzyme, with each “turn” of the enzymatic cycle, manipulates DNA expression in a way that adds time to one’s life!

NAD+ levels decline with aging and represent a fundamental, systemic cause of aging.<sup>5</sup> Falling NAD+ levels mean fewer “coins” in the “parking meter” represented by SIRT enzymes, which in turn means reduced life span, as age-accelerating genes are expressed without regulation.

Nicotinamide riboside has been scientifically proven to maintain robust levels of NAD+ in cells, thereby **both** supporting vital cellular energy functions **and** activating the anti-aging enzymes SIRT1 and SIRT3.<sup>43,63</sup> Research has demonstrated that nicotinamide riboside supplementation is capable of reversing many of the age-accelerating changes induced by falling NAD+ levels.<sup>43</sup> This is why the discovery nicotinamide riboside is so essential for any serious longevity regimen.

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