Date: October 29, 2016,  
Re: RevGenetics Memo

This document is copyrighted by RevGenetics 2016, and by downloading it and using it you agree that all information is considered a "Fair Comment" or Personal Opinion of the author(s) at RevGenetics LLC along with the full copyright and intellectual property rights terms here: http://www.revgenetics.com/terms. You may distribute this document freely for personal and commercial use as long as you do not modify it in any way and provide a link back to the following website: http://www.revgenetics.com/can-nmn-truly-reverse-aging/.

**Nicotinamide Mononucleotide**  
*Can NMN truly reverse Aging?*

The available scientific literature has clearly described a decline in the level of Co-enzyme Nicotinamide Adenine Dinucleotide (NAD+) in both murine (mice) and human studies. It is a direct function of the aging process as shown in multiple different studies. As the level of NAD+ decreases, the body starts to decline in numerous ways.

As an example, type II Diabetes (T2D) has the most new cases diagnosed between the ages of 45 to 64 as this decrease in NAD+ starts to manifest itself. This lower production is revealed elsewhere, particularly in the form of increased oxidative stress, inflammation, poorer immune response, and lower lipid (fat) metabolism, which is why we tend to gain weight as we age. Supplementation with Nicotinamide Mononucleotide (NMN) has been shown to ameliorate all of these age-related conditions, including providing impressive hepatic (liver) insulin sensitivity improvement.

NAD+ has been shown to be essential for supporting bodily functions by enhancing insulin sensitivity, improving energy metabolism, and improving stress resistance. It also participates in genome protection through DNA repair, is neuroprotective, and is required for SIRTUIN activation.

SIRTUIN genes act as an anti-aging gene in yeast, and in murine studies, one of the activators for the SIRTUIN SIT1 (signaling threshold regulating transmembrane adaptor 1) called resveratrol has been shown to activate mitochondrial biogenesis—and more mitochondria in the cells mean more available energy for the cell to function and conduct repairs.

In another murine study, age-related arterial dysfunction in older control (OC) mice versus young control (YC) mice showed that the OCs had impaired carotid artery
function compared to YC at only 60% compared to 84%, respectively. Treating with NMN resulted in restoration to 86% in OC. There was also an improvement to the elasticity of the blood vessels (improved elastin), along with reduced stiffness (decreased collagen-1), lowered aortic pulse wave velocity, and decreased chemical markers (nitrotyrosine) for oxidative stress. The OCs essentially became YCs in all but age.

In Dr. David Sinclair’s 2013 study he observed that “NMN was able to mitigate most age-related declines in mice”, and that “treatment of old mice with MNM reversed all of these biochemical aspects of aging”. He concluded that “enhancing NAD+ biosynthesis by using NAD+ intermediates, such as NMN and NR (Nicotinamide Riboside), is expected to ameliorate age-associated physiological decline”.

This has precipitated dozens of studies since that are focused on investigating NMN supplementation to treat cardiovascular disease, diabetes, obesity, life extension, cancer, Alzheimer’s disease, Parkinson’s disease, and many more.

Regarding function, NAD+ operates in a way akin to resveratrol and other polyphenols but is considerably more effective (on the order of ~100 times). It can act on (disable/detach/destroy) the proteins which inappropriately connect themselves to the histone proteins that form the latticework upon which the DNA winds itself. This appears to be a large factor in the aging process and supplants antedated prior theories about mutations being the cause.

Imagine, if you will, a strand of DNA, appropriately folded and functioning perfectly. Suddenly gene modifying proteins start to spawn because there is insufficient NAD+ to scavenge the oxidative radicals.

To understand this, think of these nasty proteins as “on” switches. They latch onto the DNA molecule’s receptors; fortunately, most of them attach to DNA that has no specific function—what we call the “junk DNA”—but periodically they will attach to something important.

At this point, it overrides the internal instructions and turns on inappropriate functions. All DNA is coded to create all of the cells in the body upon need, but how useful would it be if a brain cell suddenly had instructions turned on that told it that it was now a liver cell?

NAD+ can detach these invasive and detrimental gene modifiers, allowing the over-active gene to return to its normal quiescent state, only turning back on when truly required. In proper concentrations, as in our youth, it can destroy these proteins before they can do any damage at all. If the gene modifiers have already invaded,
research shows that it can stop the effect being expressed in and on the DNA. Better yet, it appears to arrest the progress of the disease state, allowing DNA to reverse itself to a normally healthy condition.

That being said, NAD+ is far too big a molecule to be able to penetrate a cell wall. It can neither access the DNA nor enhance the effect of the mitochondria (by making energy more available) in its final form. While these are primary functions for NAD+, NAD+ genesis needs to take place within cells.

Taking NAD+ as a supplement will do absolutely nothing for your health. It will pass through or be digested, resulting in slightly more expensive urine, but very little else. However, the much smaller precursor molecules (such as NMN and NR), can easily penetrate the micro-pores for chemical exchange in cell walls. So, as long as the mechanism for making NAD+ is intact inside the cells, the body can make all the NAD+ it requires.

This occurs primarily through two distinct metabolic pathways in our bodies, including either the Tryptophan or the Nicotinic Acid (the B-vitamin Niacin) derived de novo pathways, and/or the nicotinamide, nicotinic acid, and/or nucleoside salvage pathways, incorporating both nicotinamide riboside and nicotinic acid riboside.

The first one, the De Novo pathway, gets its name from the Latin meaning “from scratch” or “from the beginning”. Nucleotides are derived from constituent precursors such as tryptophan, which we’ve mentioned previously. It is responsible for about 15% of our NAD+ production throughout our lives.

The second path is called the Salvage pathway. It quite literally salvages nucleosides and bases whenever DNA and RNA are broken down; it also makes up a part of the body’s ongoing energy generation process.

The Salvage pathway is responsible for the remaining 85% of our NAD+ requirements. There is a problem with this pathway, however, because of a rate-limiting enzyme named Nicotinamide phosphoribosyltransferase, aka NAmPRTase or Nampt.
Nampt is like an over-ambitious traffic cop, working a multi-lane four-way intersection with broken traffic lights, which only allows one car to pass at a time, and the next one can’t start moving until the first one completely clears the intersection. It slows down everyone, creating more problems than it solves.

Once NAD+ is “used” it becomes NAM (Nicotinamide), but because of the Nampt restriction, it requires a full 8 hours to return to peak NAD+ levels. Like NAM, Nicotinamide Riboside (NR) is processed through the Salvage pathway, and takes just as long, 8 hours, to reach peak levels.

In contrast, NMN completely bypasses the Nampt bottleneck and can reach peak levels in just 30 minutes. Clearly this is a significant advantage particularly as we age and our ability to produce NAD+ diminishes.

Consider that between ages 0-10 we produce up to 300% more NAD+ than we need since our bodies are growing quickly. As we approach age 45, the production has decreased to about 100% of our needs. Beyond that, and for the rest of our lives, the NAD+ production drops below our bodies’ requirements whereupon deterioration sets in and our systems begin to fail. Until we die, we are always short by about 20% of our actual needs after age 50.

By providing adequate precursors to NAD+ formation, we can bypass the restricted or compromised Scavenger pathways and instead take advantage of the underutilized De Novo pathway. Even if that doesn't result in life extension (though it should), a normal lifespan will likely be much more enjoyable and free of the debilitating disease usually associated with age. But without NAD+ and AMP (Adenosine Mono-Phosphate) in sufficient quantity, all of this rebuilding and maintenance comes to a grinding halt, and we age.
In the liver, the preferred substrate for NAD+ building has always been tryptophan which provides the highest concentrations of this essential co-enzyme. It is important to note that NAD+ is the key to communicating between the cell nucleus, ultimately driving cell activity and the mitochondria which provide the energy required by the cell.

**What Works**

It is interesting to note that some things work better than others, which only makes sense.

- NAM is plentiful, and can enter cells with relative ease, but is dependent on Nampt for conversion into a useful NAD+ molecule
- NR taken orally is largely ineffective. It is digested and becomes NAM, thereby limiting its efficacy. Introduced directly into the bloodstream it bypasses the Nampt restricting enzyme, but unless using an I.V. drip, you would need to be constantly injecting nicotinamide to make it effective
- NMN taken orally quickly elevates the NMN levels in the bloodstream and maintains the elevated levels much longer than NAM, NA, or NR.

In this chart, you can see that the oral dose was effective in as little as 10 minutes in the liver. After 30 minutes had elapsed, not only had it more than doubled the amount available in the liver, but it had manifested itself in a major muscle (soleus) at the back of the leg, vital for standing, walking, or running, ready to supply more energy.

This demonstrates that the NMN makes it through the digestive system, the liver, and then the bloodstream intact so that it can be metabolized in muscle tissue in just 30 minutes. The de novo pathway is more than capable of handling our NAD+ needs,
bypassing the Nampt restrictions in the salvage pathways, as long as the precursors are available.

**Making the Point**

A murine study demonstrates that NMN quickly disseminates from the gut to the bloodstream in just 2-3 minutes, and is taken up (cleared from the blood) into tissues in just 15 minutes. The salvage mechanism simply cannot match this efficiency.

That same study further revealed that long-term dietary supplementation of one group of identical mice, divided into two groups, Controls (C) on an ordinary diet, and subjects (S) who received Nicotinamide (NMN), showed steady aging and anti-aging, respectively. Controls gained weight whereas Subjects lost fat and gained lean muscle mass; C’s energy metabolism decreased, S’s metabolism increased, as shown in the accompanying chart.

NAD+ and the SIRT1 gene were found in considerably higher concentrations than in young mice. This also resulted in higher energy and activity levels and improved health with no detectable deleterious side effects or toxicity using both blood chemistry panels and urinalysis. Notably, there was no difference in overall lifespan, but health was better throughout the studies.

Mice on an NMN-enhanced diet experienced a switch in energy metabolism from glucose to fatty acids. Regular energy requirements are met with less metabolic strain using fats as the source. This avoids all the peaks and valleys in blood sugar levels, restoring a more conventional metabolism that animals experience, and which was our human heritage before we discovered how to make sugar.

Modern nutrition is slowly coming to the realization that up to 75% of our energy requirements should come from dietary fats, 20% from proteins, and only 5% from carbohydrates—but not any carbs sought out deliberately—just incidental ones from eating a quantity of healthy greens for their vitamin content.
Carbohydrates spike sugar levels and contribute to insulin resistance which, going back to the point made at the beginning is the chief cause of T2D when our systems start to fail around age 45, and we can no longer control our blood sugar levels. Fully half of the U.S. population has T2D or pre-diabetes, and most of them don’t know it because they are still healthy enough to cope with the stress.

The reasoning is simple. Our bodies require **essential fats** and require **essential proteins** that we cannot manufacture, but there is no nutritional requirement for carbohydrate in our diet. Our bodies are capable of making any carbohydrates that we require, so there is no “essential” component anywhere in the carbohydrate spectrum.

Sarah Hallberg, Ph.D., an Obesity Doctor, gave a TED Talk on this very subject, and it is quite worthwhile to review at your convenience.

Nevertheless, as a consequence of fat metabolism, the mice use more oxygen because they are more physically fit, healthy, and active. After 12 months on the regimen, the NMN subjects were exhibiting energy levels, and food & water consumption levels, similar to mice that were six months younger.

**Human Studies**

Mice can’t have all the fun, of course, so human studies (conducted in Tokyo’s Keio University School of Medicine and the Washington University School of Medicine) are currently in progress (concluding June 1st, 2020) to determine change in insulin sensitivity, and to determine change in beta-cell function over the course of two years with NMN supplementation.

Researchers also expect to gather results on control of blood sugar, dilation of blood vessels, changes in both blood lipid and body fat levels, and changes in the markers for cardiovascular disease.

**Non-toxic**

NMN is available in vegetables, mushrooms, meat, and shrimp but trying to obtain sufficient through diet alone would be problematic. Studies dosages have been about 50mg - 250mg. The FDA suggests that a 150 pound (68kg) human would
require about 560mg per day. The difficulty is that you would have to eat about 100 pounds of edamame, 1,800 pounds of broccoli, or similarly impossible amounts of cucumber, cabbage, avocado, tomato, mushrooms, raw beef, or shrimp.

(continued)

**Raised Eyebrows**

The ongoing theme of this research has been surprising. Quotations (unattributed) are constantly spawning from researchers, indicating that the promising (and sometimes astonishing) results are not diminishing. Here are some examples:

- “NMN supplementation mimics exercise.”
- “NMN restored the mitochondrial homeostasis and key biochemical markers of muscle health in a 22-month-old mouse to levels similar to a 6-month-old mouse.”
- “NMN-supplementation can induce reversal of glucose intolerance.”
- “…the cells of old mice were indistinguishable from young mice after just one week of treatment.”
- “Surprisingly, just one dose of NMN normalized impaired glucose tolerance.”
- “raising NAD+ levels in old mice restores mitochondrial function to that of a young mouse.”
- “Remarkably, NMN administered to FXN-KO mice\(^1\) restores cardiac function to near-normal levels.”
- “NMN treatment reduces brain cell death and oxidative stress. These results further support the neuroprotection of NMN/NAD+.”
- “NMN significantly increased the level of NAD+ in the heart. NMN protected the heart from I/R injury.\(^2\)”
- “Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice.”
“NMN treatment reduces brain cell death and oxidative stress.”

“NMN could restore cognition in Alzheimer’s Disease (AD) model rats. The beneficial effect of NMN is produced by ameliorating neuron survival, improving energy metabolism and reducing ROS accumulation. These results suggest that NMN may become a promising therapeutic drug for AD.”

The Takeaway

NAD+ levels diminish as we age. This exacerbates a decline in our health, but ongoing studies indicate that this can be ameliorated through NMN supplementation to the levels of a much younger individual.

The health benefits under investigation strongly suggest that there are significant benefits to be derived from NMN supplementation which, even if they do not extend life expectancy, should result in improved quality of life with fewer infirmities and disease processes.

You may still only live to age 80, but you’ll have stronger bones, more energy, better eyesight, a clear brain and vivid thought processes. There will be no need to sit in a rocking chair waiting for a relative to visit.

If life is extended, then you can remain active and healthy. If not, instead of spending the last two decades being sick, you can continue normally until you reach the end of the trail, still in good health, or at worst, only infirm for a short period at the end, rather than decades.

Finally

All of the precursors for manufacturing NAD+ are effective at raising NAD+ levels in the liver, but this does not distribute uniformly throughout the body, especially to those organs or tissues without direct access to the bloodstream.

Of all the precursors for NAD+, only NMN is both stable and available to cells through the bloodstream, and does not need to deal with the Nampt enzyme that restricts NAD+ formation.

This research is very promising, and of benefit to us all. Keep an eye on developments, because it will eventually affect you, no matter what your age.
[1] Frataxin deficient Knock-In/Knock-Out (KIKO) mice specimens with cardiac deficiency

[2] ischemia/reperfusion (I/R) injuries include myocardial infarction, stroke, and peripheral vascular disease.