# The Revolutionary Science of Aging and Longevity

**By Dr. Joseph Mercola | mercola.com**

## STORY AT-A-GLANCE

- Two scientifically demonstrated benefits of fasting are the suppression of the mammalian target of rapamycin (mTOR) and the activation of autophagy, both of which play a role in disease prevention and longevity
- After the age of 30, extrapolations from animal studies suggest the longer you're able to incorporate some form of regular fasting across your life span, the better
- When added to a low-calorie diet and healthy lifestyle, NAD boosters such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) appear to have a magnifying effect, allowing you to maximize your benefits
- Sirtuins are proteins that act as environmental stress sensors and are responsible for longevity. Activating sirtuins is one way to increase longevity in yeast and worms. One compound found to activate sirtuins is NAD. Another is resveratrol
- Research led by David Sinclair, Ph.D., has demonstrated it's possible to reprogram cells, restoring their original youthfulness, and in so doing, reversing blindness by rejuvenating the nerves in the retina

David Sinclair, Ph.D.,[1] is a professor of genetics and co-director of the Paul F. Glenn Center for the Biology of Aging at Harvard Medical School. Generally recognized as one of the thought leaders in the science of how to improve our life span and health span, Sinclair earned his Ph.D. in Sydney,

Australia.

After working with Leonard Guarente at Massachusetts Institute of Technology as a postdoctoral researcher, he got his own lab at Harvard in 1999, where he's been teaching aging biology and translational medicine ever since. Sinclair has also written a book, "Lifespan: Why We Age – and Why We Don't Have To," which is scheduled for publication on September 10, 2019.

## Fasting is part of the longevity solution

Sinclair's book covers several important strategies that can help slow down the biological clock, including calorie restriction and intermittent fasting. Two of the scientifically demonstrated benefits of fasting are the suppression of the mammalian target of rapamycin (mTOR) and the activation of autophagy.

As noted by Sinclair, while fasting itself is not revolutionary, having roots dating back more than 5,000 years, what's revolutionary "is the discovery of the biochemical pathways that underlie this protection against disease and aging." Like me, he's a fan of time-restricted eating, where he simply skips one meal (breakfast) each day.

*"There are other diets that other people have found to be effective in terms of improving biology and biochemical markers,"* Sinclair says. *"One is the 5:2 diet … That one is also quite doable …*

*More extreme are those diets where you [fast] for a whole week every couple of months or every few months … My view is that that's probably going to work the best if you can do it because it doesn't just trigger the short-term pathways that we've been studying in my lab.*

*A week of fasting will really [trigger] the body to start*

*consuming its own protein … That's what autophagy is. It's the consuming of biological material, which is typically a protein. In talking with people who've done these fasting regimens, after about three days, something different starts to kick in. People who try this tell me that they have a feeling of euphoria. They definitely get an added boost …*

*We've been studying in my lab for the last 20 years genes that respond to diet, to fasting and calorie restriction. The upshot of it is that our bodies respond to adversity or perceived adversity. They turn on these defensive pathways. It changes a bunch of genes that switch on to defend our bodies …*

*These defenses of the body are extremely good at protecting us against diseases — from diabetes to cancer, heart disease, even dementia and Alzheimer's. These are things that modern medicine has struggled to combat. This seems to be a very simple way to get the body to fight those diseases."*

## At what age should you start fasting?

As for when to start, animal studies suggest the younger you are when you start, the better. For humans, this would, of course, have to be done within reason. It would be downright foolhardy to put an infant on a fasting regimen, for example.

Teens and young adults in their 20s are also not candidates for fasting, Sinclair says, as "There's still a lot going on in their bodies and their brains." After the age of 30, however, extrapolations from animal studies suggest the longer you're able to incorporate some form of regular fasting across your life span, the better.

As a general rule, intermittent fasting involves fasting for 12 to 16 hours a day, which will typically necessitate eliminating either breakfast or dinner. If you eat dinner,

you'll want to make sure you do it early enough – at least three hours before bedtime. I try to eat my last meal three to six hours before bed.

One of the reasons for this advice is because avoiding late-night eating will increase your nicotinamide adenine dinucleotide (NAD+) levels, which are important for a variety of bodily functions.

Importantly, it will also reduce nicotinamide adenine dinucleotide phosphate (NADPH), which is essentially the true cellular battery of your cell and has the reductive potential to recharge your antioxidants. The largest consumer of NADPH is the creation of fatty acids.

If you're eating close to bedtime, then you're not going to be able to use the NADPH to burn those calories as energy. Instead, they must be stored in some way. To store them, you have to create fat, so you're basically radically lowering your NADPH levels when you eat late at night because they are being consumed to store your extra calories by creating fat.

*"I tend to snack at night, so it's my downfall,"* Sinclair says, *"but yes, to be able to have that fast overnight, that'll boost your NAD and NADPH levels. These are all good things. They turn on the enzymes that we study called sirtuins. They need NAD to function. You can use the whole night to ostensibly repair your body and protect it from what happens during the day."*

## Everything in moderation

An important part of Sinclair's book delves into the balance between anabolism – the building of muscle tissue – and catabolism, the tearing down and repair of muscle. Counterintuitively, when you fast, growth hormone levels increase, even though there are no nutrients available. Sinclair explains:

*"Insulin-like growth hormone (IGF-1) and growth hormone itself, in the short run, don't seem to be healthy, at least in animal studies. Nir Barzilai of Albert Einstein College of Medicine has studied centenarian families. What he's found, in particular [in regard] to IGF-1, is that some families can have high levels of IGF-1 but still live a long time.*

*The reason for that is that they don't have the IGF-1 receptor as active … [I]f you're not responding to these hormones, it doesn't really matter how much your body produces. It'll still have an effect that mimics the benefits you want. It's interesting actually that the growth hormone is stimulated by fasting … I'm unaware of exactly why.*

*But we know that fasting doesn't lead to bigger animals. It's actually the opposite. It could be — now I'm just speculating, but I think it's worth discussing and thinking about — that the short-term bursts of hormones may help the body recover from injury. But those little spikes don't last long so that you're not having any downsides …*

*If I was to summarize everything that I've learned over the last 30 years: 'Everything in moderation, and don't do anything too consistently.' … Your body needs to be primed and then allowed to relax; challenged and then allowed to relax.*

*These diets and these growth hormone spikes, I think they're good. You just don't want them on all the time, because then your body doesn't have a chance to recover and you don't get the long-term benefits."*

# The case for exercising in a fasted state

A tangent to this is the idea that the ideal time to do strength training is right before you have your first meal after a 16- or 18-hour fast. In other words, exercising while

still fasting.

The reason for this is because your growth hormone is already activated, allowing you to reap maximum benefit from the anabolic stress of the exercise, which increases peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial biogenesis. As noted by Sinclair, this is "the cutting edge of thinking."

*"Again, in the full disclaimer, we're discussing the cutting edge of science, so we don't fully know the answers to this. But what makes sense to me is that we don't want too much protein in our lives. We don't want to eat a steak at every meal.*

*Because what we've learned through the work of David Sabatini and many others in the field is that … inhibiting the mTOR pathway by having a lack of certain amino acids is healthy and does lengthen lifespan in animals.*

*But does that mean that you shouldn't eat protein? Absolutely not. There are times when eating proteins is important. Same for testosterone. Same for growth hormone. Now we're getting into the nitty-gritty. If you are pulsing these things, when do you do them together and when do you do them apart?*

*Let me talk about what I do personally because that's actually a better way to approach the discussion. If I'm going to have a steak – I try to be a vegetarian – but let's say I'm going to have a protein shake, I'm going to do that just before or just after I've exercised.*

*But then I'm also going to have a period in the week where I don't have a lot of protein … I think … that a little bit of stress every day and a lot of stress once in a while is a great combo."*

# The importance of NAD boosters

In his book, Sinclair also discusses the importance of glycine, the shortest and most common amino acid in your body. In the past, people got plenty of glycine from eating bone broth and connective tissue, but most people today are not in the habit of eating homemade bone broth.

As a result, many are not getting enough. Unfortunately, glycine is all the more important these days, as our fructose consumption has dramatically increased. Sinclair explains:

*"This is a big question in my field. Just to take a step back, my field and a lot of what my book is about are [about how] to trick the body into [thinking it's] hungry and having exercise. One of the molecules that do that is NAD.*

*NAD stands for nicotinamide adenine dinucleotide and we have it in our body. As we exercise and get hungry, it goes up. As we get older, it goes down. It's needed for life. It's also needed for turning on these defensive enzymes called sirtuins.*

*Now, to raise NAD levels, what we've done in my lab to mice for the last decade is we give them precursors to NAD. We give them molecules like nicotinamide riboside, or NR, or nicotinamide mononucleotide, also known as NMN …*

*When times are tough, we're hungry or we've exercised, NAD levels will go up and turn on these defenses. That's why when you take a molecule like NMN … what we think is happening is that you're tricking your body into thinking that it's [had] exercise or that it's hungry because the NAD levels will go up.*

*So, you get the protective benefits … without actually having to necessarily exercise or diet … NMN is what I take each day. I take a gram of it. The thing with NMN is that it has this nicotinamide group on it. It hangs off the main part of the*

*chemical and it's the first bond to break. We see in animals and even in humans that the levels of nicotinamide go up quite rapidly after taking NMN or NR.*

*Too high a level of nicotinamide is not good, in part because the nicotinamide gets excreted through the kidneys. That happens because it becomes methylated into methyl nicotinamide. Methyl nicotinamide had been used for years as a marker of all sorts of things …*

*But the concern … is, 'Is this drain of methyl nicotinamide a problem?' The methyl groups are needed for the body. We need methyl for a whole range of things, including antioxidants. As a precaution, I take trimethylglycine so that I continue to give my body a source of methyl groups …*

*I take it as a precaution because I know that trimethylglycine is not going to hurt me … The other thing is trimethylglycine, also known as betaine, is very good for [human cells], including protecting them against stress. I don't see any downside … The upside is that I'm preventing my body from being drained of methyl groups."*

None of this is to say you'll be able to simply take a supplement or two and live a long life while eating junk food and being inactive. They can improve your condition if you're overweight and don't exercise, but they're not a panacea or replacement for a healthy diet and lifestyle.

However, when added to a low-calorie diet and healthy lifestyle, NAD boosters such as NR and NMN do appear to have a magnifying effect, allowing you to really maximize your benefits.

There are other NAD boosters beside NR and NMN, and open questions regarding methods of administration of NR and NMN that may influence their efficacy. All of that is discussed in the interview so, for more details, please listen to it in its entirety, or read through the transcript. I go into detail as

to why I believe using the NAD+ molecule itself is likely a far better strategy than using precursors. It is what I am currently doing for my own program.

## The theory of xenohormesis

Sirtuins, which much of Sinclair's studies are focused on, are proteins that act as environmental stress sensors and are responsible for longevity. In simple terms, you could refer to them as longevity proteins. Evidence suggests sirtuins work by suppressing DNA expression. As explained by Sinclair, activating sirtuins is one way to increase longevity in yeast and worms.

One compound found to activate sirtuins is resveratrol. However, once activated, sirtuins require NAD+ as a co-enzyme, and if it isn't available, it won't work. Sinclair and his team screened about 18,000 compounds to identify activators, and found you need the SIRT1 gene for it to work – it's not just an antioxidant effect.

*"We published 21 activators in that first paper in the Nature journal, 2003. Resveratrol was the best one we had at the time. It got the most attention because the red wine story was pretty funny and interesting to the media. But there were others that were very close to resveratrol in structure and potency.*

*Quercetin and fisetin are plant molecules as well. They're all produced in response to stress … dehydration or ultraviolet (UV) light. They seem to have benefits on organisms [that] consume them.*

*Interestingly, what has later been discovered, though rarely acknowledged, is that these same molecules work on killing senescent cells … the 'zombie cells' that accumulate in your body and cause havoc. Now, others have shown that quercetin … have senolytic properties, same with fisetin. But what's not*

*recognized typically, or admitted, is that these molecules were discovered 15 years ago to also be SIRT1 activators …*

*The hypothesis Dr. Konrad Howitz and I came up with, which we published in Cell [in] 2005 … is called xenohormesis. It's the idea that we've evolved to sense our environment, and molecules produced by plants and bacteria in our environment when they're stressed.*

*If we consume those or put them on our skin, for example, our bodies will recognize those. We've evolved to sense our world around us. That's a very good way of getting a heads up if your plants are running out of nutrients or the water table is drying up …*

*That can explain why so many molecules from the plant world have given rise to medicines and why some molecules, like resveratrol and quercetin, fisetin, even aspirin, have remarkable health benefits and target many different enzymes in the body that seems to be well beyond what coincidence could explain …*

*It's thought that a little bit of heat, a little bit of cold, a little bit of hunger, some exercise, some hypoxia, lack of oxygen in your body, these are all ways of activating these defense pathways … such as sirtuins … the mTOR, which lower amino acids, particularly leucine and arginine, and the AMPK pathway … these are the main three defensive pathways. There are others.*

*But what's downstream of these pathways are things like heat-shock proteins and transcription factors that turn on DNA repair enzymes … Here's the good news: We used to think we had to understand everything those sensors do to be able to understand aging and be able to live longer.*

*But what I've been arguing for many years now is that we don't need to fully know what they do … As long as we can find the right nodes in the cell, to turn them on in the right ratios*

*at the right time, the body has evolved to take care of the rest.*

*We're getting to the point … where we know what these nodes are. We have the tools to tweak them. We can also change them naturally by fasting and exercising. We can change them with molecules that we can ingest or inject. But now, the cutting-edge is, when do you apply them, how much and in what combinations? That's really what people like myself … are onto right now."*

## The importance of DNA repair

Another strategy for increasing NAD+ is to avoid things that use it up, such as exposure to electromagnetic fields (EMFs). One of the primary DNA repair enzymes inside your cells is poly-ADP ribose polymerase (PARP). PARP repairs single- and double-stranded DNA breaks and, in so doing, it will use up 100 to 150 NAD molecules for each break.

The more DNA breaks you have, the more NAD is being used up in the repair process. EMF exposure activates PARP and decreases NAD. So, by limiting EMF exposure, you can, by default, increase your NAD, simply because you're not activating PARP as much.

*"PARP enzymes are DNA-repair protein. The problem is when you hyperactivate this protein … There are actually more than 14 different PARPs. They do drain NAD quite effectively. In fact, in my lab, we've discovered another PARP that, when you have inflammation, drains NAD as well. It does make sense to slow them down … and in some cases, inhibit … their overuse of NAD,"* Sinclair says.

Again, the best way to do that is by avoiding insults, such as EMFs, that activate the PARPs. "Then you get the benefits of low DNA damage and the benefits of high NAD," Sinclair says, adding:

*"Long story short, you want to activate PARP, but not too much … [Even] more interesting, I think, is how do you keep your levels of DNA double-strand breaks to a minimum? I think that's one of the main keys to longevity.*

*There are two reasons: One is that double-strand breaks drain NAD. The second … is the idea that DNA double-strand breaks also disrupt the cell's epigenome, the storage of the information that we get passed down from our mothers and fathers, mother and father, and the packaging of the DNA …*

*Basically, what happens is, if you have a broken DNA, proteins such as the sirtuins will leave their normal sites where they're regulating genes and go help repair with PARP. But then they don't all find their way back to where they came from. Some of them get lost and distracted.*

*Over time, what we see is that these proteins that are essential for maintaining cellular identity and function will be lost. We see that in yeast cells. Yeast cells get old because they're moving between breaks and back again to genes."*

# The epigenetic noise of aging

One of the most fascinating aspects of Sinclair's book is the section on how to resolve some of this epigenetic damage, which accumulates through aging. Using the clustered regularly interspaced short palindromic repeats (CRISPR) technique, certain transcription factors were spliced into blind mice, thereby restoring their vision through epigenetic resurrection. Sinclair explains:

*"This is a sneak preview of what, hopefully, will be published later this year … We've discovered what we think is very strong evidence for … epigenetic noise as a cause of aging … What does that mean?*

*Let's just quickly do a biology lesson for those who haven't been in high school for a while … [The] epigenome is the organization of DNA. The epigenome tells the cell that they should turn on this gene to be a nerve cell, and in a liver cell … Cells inherit that [epigenetic] information just as much as they inherit their DNA.*

*In my book, what I'm proposing is that … genomic and epigenomic information are quite different. The genomic, the DNA, is 'digital,' which is very well-preserved and can last a long time. We know that DVDs last longer than cassette tapes.*

*The problem for the epigenome is that it's 'analog' information. Anyone who's had a cassette tape or a record knows that you can pretty easily scratch these or lose the information. You can [also] scratch a DVD and lose the information.*

*We think aging is similar to those scratches; that the information to be young again is still largely in our bodies. Our cells can access that information by metaphorically polishing the DVD … so the cell can read the right genes …*

*With that in mind, let me explain what we've discovered. We have a metaphorical way of scratching a mouse's epigenome: We cut the DNA. We create these double-strand breaks [and] let the cell heal … so there's no change to the digital information. But what we see is the process of proteins moving around and trying to repair that DNA.*

*It eventually introduces this epigenomic noise, and the genes that were once on, many of them get turned off. Those that were once off come on. Liver cells start to lose their identities. Skin cells start to lose their identity. The consequence, we think, is aging.*

*We will hopefully publish a paper that shows that if you create this noise in a mouse, it will go through accelerated aging … Second of all, we have mice now that we can change the*

*rate of aging in … The third thing is if you can give an animal something, then you can, with that knowledge, take it away. That's what we've done …*

*We wanted to reprogram cells. The genes that were … on, now they go back off and vice versa … What we find is that by using these three Yamanaka factors, you can find the original information in the cell that tells it to be young again.*

*Those genes switch, and the cell behaves like it's young again. In the case of the retina, we have preliminary results [showing] we can restore eyesight by rejuvenating the nerves in the retina to be young again."*

## More information

Eventually, Sinclair's goal is to identify ways to reprogram all cells in the body, such that they not just act younger but literally are younger on a molecular level. "In my career, I've seen a lot of cool stuff. I haven't seen anything this cool before," he says. Clearly, there's extraordinary potential to extend the human life span beyond the current 120 limits.

In his book, he proposes there's no built-in biological requirement for death, and that, theoretically at least, you could live hundreds of years. To learn more about Sinclair's research, and the science behind aging and the potential for reversing aging, be sure to pick up a copy of his book, "Lifespan: Why We Age — and Why We Don't Have To."

*"We could see a world where people do choose to be genetically modified," Sinclair says. "It's their choice, right? I don't think we can easily go in and modify children even though that's now being done, unless it's life-threatening, of course. But adults know that they should be able to have a choice if they're safe and it's approved, then they should be able to do that.*

*Maybe there will be a day when we are able to carry these Yamanaka genes in our body. And when we get sick or we have an injury … then we get an IV that turns on those genes for a month. We recover and rejuvenate, then we turn them off again until we need them again. That would be a pretty wild sci-fi future, but both signs are pointing to at least the biology being possible …*

*I hope people who read the book come away with a new view of what's possible. Some people who have read it tell me that it's changed the way they look at their own lives. That's what I wanted to do. I think we forget how important this topic is, that we can do things right now to alter the course of our lives."*

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