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Take Control of Your Health

Simple Strategies That Will Help You Live Longer

Analysis by Dr. Joseph Mercola ✔ Fact Checked | October 08, 2023

STORY AT-A-GLANCE

- Supercentenarians are the rare individuals who have made it to the age of 110 and beyond. At any given time, there are only 50 to 80 supercentenarians in the entire world. In the U.S., an estimated 120,000 people make it to 100, but only 20 of them make it to 110
- What sets them apart is that, up until the ages of 105 to 108, they've maintained the health of someone in their 70s and 80s. They have no age-related diseases, and typically die from sudden onset immune failure
- In many respects, supercentenarians age normally, while the rest of us age at an accelerated rate. The basis of the book, "The Switch: Ignite Your Metabolism With Intermittent Fasting, Protein Cycling, and Keto," is essentially how to normalize your aging rate, thus allowing you to optimize your life span
- Cyclically activating and deactivating the mTOR pathway to intermittently trigger autophagy is a key element that will increase your longevity. Time-restricted eating and other fasting regimens accomplish this. Fasted exercise can further boost results
- NAD+ is one of the most important longevity molecules that we know of. NAD+ is a coenzyme needed by longevity-related enzymes called sirtuins. It's also required for DNA repair, but levels plummet with age, necessitating ways to boost NAD+ levels. Strategies include time-restricted eating, fasted exercise and supplementation

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If you're interested in healthy living, you won't want to miss this interview with antiaging scientist James Clement, author of "**The Switch: Ignite Your Metabolism With Intermittent Fasting, Protein Cycling, and Keto**," While a lawyer by trade, he has since transitioned into a full-time research position, running his own antiaging research laboratory.

From Lawyer to Full-Time Researcher

Clement wrote "The Switch" because he saw that many still don't understand the basics of health and longevity. The "switch" refers to the switch between activating and deactivating the mammalian target of rapamycin (mTOR) pathway, which is the central topic of discussion here. His book also covers how to upregulate your mitochondrial function and other important pathways for health and longevity, such as NAD+.

> *"For [as long as] I can remember, I've always been interested in longevity,"* Clement says. *"I just didn't know that there was a field that dealt with [longevity] until Durk Pearson and Sandy Shaw's book, 'Life Extension: A Practical Scientific Approach,' came out in 1982.*
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> *I happened to be a third-year law student at the time, married to another law student. As soon as I read the book, which I did in like two days, I said, 'I'm going to be a molecular biologist.' She jokingly said, 'No. You aren't.' But I did start reading molecular biology. I became very passionate about keeping up with antiaging science.*
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> *I was lucky enough in 2009 to get on the board of the first direct-to-consumer genome company called Knome that George Church had co-founded. I had my own whole genome sequenced in 2009. George was the scientist who read me my interpretation of my genome.*
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> *We started talking about aging. I found out that he had this similar passion. We came up with a project called the Supercentenarian Research Study. That sort*

of launched my becoming a full-time scientist as opposed to a lawyer and entrepreneur that I've done previously …

We were a couple of years into the supercentenarian project. I was starting to open my own lab. I started a vivarium and eventually added 1,200 mice that I raised by myself with a couple of interns. At that time, I approached George and asked him, 'Do you think it would be beneficial to my credibility, career and knowledge to enroll in a Ph.D. program?'

George kind of looked at me and said, 'You're doing projects that grad students would give their right arm for. You're already reading 10 to 20 scientific papers a day. You're involved in writing up research papers. This is what a scientist is. This is what they do. You don't need to go work for someone else to learn these processes.' So, I stuck with what I was doing."

60 Minutes Interview With Harvard Geneticist Professor George Church

What Sets Supercentenarians Apart?

Supercentenarians are the rare individuals who have made it to the age of 110 and beyond. According to Clement, there are only 50 to 80 supercentenarians in the entire world at any given point. In the U.S., an estimated 120,000 people make it to 100, but only 20 of them make it to 110.

As Clement began working with these supercentenarians, he realized that what set them apart was the fact that, up until the age of 105 to 108, they'd really had the health of someone in their 70s and 80s. They have no age-related diseases, and typically die from sudden onset immune failure followed by pneumonia.

This suggests that improving your immune function is an essential criterion to make it past 100. Clement goes so far as to say that, in many respects, supercentenarians age normally, while the rest of us age at an accelerated rate. The basis of his book is essentially how to normalize your aging, thus allowing you to optimize your life span.

It's worth noting that while your lifestyle plays a tremendous role, there's also a strong genetic influence. Siblings of supercentenarians have a 17 times greater chance of reaching 100 years old than the rest of us, for example, and many female supercentenarians have a mutation in the IGF-1 pathway.

This makes them short in stature, so 5 feet is about the size of the normal supercentenarian woman. In men, it tends to be a growth hormone mutation that similarly makes supercentenarian men somewhat shorter than the average man. Importantly, these mutations limit mTOR and turns on autophagy, which is what gives these people such a head-start on longevity. But there are ways for the rest of us to limit mTOR and increase autophagy as well.

The Switch

The target of rapamycin (TOR), from which mTOR derives, is an evolutionary mechanism that started with bacteria. All organisms need nutrition, and the ability to make proteins and reproduce. When nutrition is scarce, as it tends to be from time to time in the natural world, the organism must venture out to seek more resources.

> *"The organisms that developed ways to hunker down and protect themselves during these times of scarcity are the ones that survived and we evolved from,"* Clement explains.
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> *"We evolved and carried with us those genes that protected bacteria, yeast cells, C. elegans worms, drosophila, mice, primates, et cetera. They all have a version of mTOR. They all go through this metabolic switch called mTOR and have an anabolistic state, anabolism, and a catabolic state, or catabolism."*

Anabolism is what allows you to grow and increase muscle mass, whereas catabolism is the process of breaking down, repairing and removing old worn-out cells. Importantly, catabolism is the phase that cells enter when resources are scarce.

The cells essentially slow down protein production and cell division at this time, and activate the process of autophagy, which gets rid of misfolded proteins and

dysfunctional organelles.

These old, worn-out proteins and organelles are recycled by lysosome, which breaks them down into their base component parts and then releases them back into the cell. These components can then be used to make new amino acids capable of rebuilding new proteins.

This natural clean-out and regeneration process is why activating autophagy on a regular basis is key for health and longevity. The same process occurs in your mitochondria, which is called mitophagy.

> *"Like all other organisms, humans, for most our evolutionary history, encountered this feast-or-famine state. Only recently, like literally the last 150 years, has food production, industrialization of farming and livestock management and refrigeration made it possible … to have a never-ending abundance, mostly of foods that we didn't evolve to eat in the first place,"* Clement says.

Why Cycling Through Feast and Famine Is so Important

One common mistake, which I also made, is continuously inhibiting mTOR. It's really important to cycle back and forth between inhibition and activation of mTOR. The anabolic state triggers cell growth, and that includes stem cells — cells that can become any cell needed, anywhere in your body.

> *"If you learn about mTOR and you say, 'I don't want cancer, and turning on mTOR full-time and keeping autophagy off leads to cancer, so I'm going to do the reverse,' then what you end up doing is not having a strong populating of stem cells, not replacing damaged tissue, and you end up losing muscle mass through sarcopenia.*
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> *I experienced this myself. I was on a vegan version of the ketogenic diet for five years. I was doing this as self-experimentation … I ended up losing a lot of muscle mass.*

But as soon as I recognized what was going on and really thought about the literature and what this meant, I realized that I was foregoing the thing that nature had previously required, which is that you go through this feast [stage]," Clement says.

"We have a whole chapter describing the different ways that you can implement this in your own life. There's no one plan. There are basically guidelines. … You can still have your pizza, your cheese, cake, ice cream, et cetera, but you can't do this day in and day out. You can't leave mTOR on [activated] and the brakes on autophagy full-time."

How to Incorporate Exercise for Optimal Results

The timing of exercise can also play a role. If you're fasting for 20 hours and eating within a four-hour window, aggressively working out about two hours before you break your fast will suppress mTOR and activate autophagy even further, increasing metabolic markers such as 5 AMP-activated protein kinase (AMPK) and decreasing insulin-like growth factor (IGF), at least in your muscle.

As noted by Clement, this strategy will actually allow you to achieve the benefits of a two- to three-day long fast.

"By and large, the average person, who is obese and on seven medications by the time they're 70 years old and has hypertension and all these problems, those people got there because they weren't paying attention to this switch," Clement says.

"These discussions about autophagy tell people essentially what to do to turn it on, but hasn't really focused much on the balance — the fact that we need both sides of this. I've also concentrated on the triggers that turn on mTOR, because if we want it on, then we want to make sure we aren't taking supplements or doing something else that tends to inhibit it …

A branched-chain amino acid named leucine, which is four times higher in dairy than it is in human breast milk, essentially locks on mTOR … Leucine is almost like a key that, alone, without any help from anything else, in sufficient quantities, will trigger mTOR activation and turn off autophagy …

Generally speaking, if you are consuming dairy or animal meat, you will likely have sufficient levels of leucine. Now, the cell also needs, for mTOR to be working fully, insulin … which means you need certain levels of blood sugar that will essentially trigger insulin to be relatively high …

Without leucine or sufficient amino acids, mTOR is going to essentially wait. That's what autophagy is actually meant to do — it's to create more amino acids by breaking down organelles and misfolded proteins to supply the cell [raw material to reuse].

It's got the sugar. It's got the energy. The insulin receptor is turned on but it lacks the amino acids. So, through a short bout of autophagy, the cell would most likely have enough to go through with cell division or protein production."

The Importance of NAD+

Overall, NAD+ may be one of the most important longevity molecules that we know of. As explained by Clement, NAD+ is a coenzyme needed by longevity-related enzymes called sirtuins. It's also required for DNA repair.

Finding data on NAD+ sorely lacking, Clement began his own research, starting with a clinical trial testing intravenous (IV) NAD+ in elderly people, in collaboration with Dr. John Sturges. Clement also underwent the treatment, which involved an infusion of 1,000 milligrams of NAD+ per day for six straight days, finding it remarkably effective for tremors he'd had since he was 20 years old.

"My hands would shake … It was just some neurological problem. It wasn't the onset of Parkinson's at 20 years old or anything else that anyone could point to.

But surprisingly, within an hour or two of starting the IV infusion, my tremors went away completely, which I had had for the previous 40 years.

I noticed later that evening that I fell asleep and didn't wake up during the middle of the night … I woke up way earlier than I normally would, completely refreshed and ready to get back to work. This was the same kind of experiences all of our elderly patients were telling us as well. We had several people who had tremors that went away.

I think [1,000 mg of NAD+] is too much for people who don't have issues that would cause incredibly severe NAD+ depletion … Your body uses copious amounts of NAD+ to detoxify alcohol, for example. In and of itself, drinking every single night of your life will drastically deplete your NAD+ levels.

There are other things that people do that can deplete their NAD+ levels. We've seen that in teenagers who get an infection, influenza or something and then all of a sudden start getting migraines.

NAD+ will totally prevent the onset of migraines for periods of two or three months at a time. People who have had multiple migraines a month who get on these iontophoresis NAD+ patches can go years without having migraines.

There are many, many symptoms of NAD+ depletion that we're just now learning. We're finding that restoring the NAD+ to healthy levels gets rid of these symptoms almost immediately."

NAD Plummets With Age

NAD+ levels plummet by the time you're 60 years old, and is nearly undetectable by the time you're 80. NAD+ is a crucial part of the longevity puzzle, as it's essential for repairing broken DNA. Broken DNA is not something that occurs once in a while.

Single-stranded DNA breaks occur about 125 times an hour in every cell of your body, and double-stranded breaks occur about 25 times per day in every cell. DNA breaks are

further accelerated if you're exposed to high levels of electromagnetic fields, which virtually everyone in the developed world are.

> *"There are lots of lifestyle practices and exposures that will increase [DNA breaks] dramatically, and you need NAD+ in order to turn on gene repair,"* Clement says.

> *"If [NAD+] is naturally going down — by the time you're 60 it's maybe 50% of what it was when you were in your 20s and 30s, and then by the time you're 70, it's 10% and then at 80, there's almost none — you can see how this huge build-up of damaged DNA in every cell of your body is potentially one of the driving forces of these morbidities that you see with aging, heart disease, cancer [and] Alzheimer's …"*

While IV NAD+ is available, it's cost prohibitive at $1,000 per IV. Fortunately, there are less expensive ways to raise your NAD+. Two precursors to NAD+ are nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), both of which are available in supplement form. NAD+ patches are also available, and all of these are far more economical than IV.

A 1,000-milligram dose of NR has been shown to double your NAD+ level. The problem is that for the elderly, doubling a grossly deficient level is not enough. In people with near-undetectable levels, the NAD+ levels need to be increased by 10 to 100 times.

So, while taking an NR or NMN precursor for six months will double your level, you may still be depleted. Clement's study revealed many older people need 4 or 5 grams a day for a period of time to restore more youthful levels, which could end up being costly at today's price of NAD supplements.

To circle back to exercise and time-restricted eating, both of these strategies will increase nicotinamide phosphoribosyl transferase (NAMPT) by about 30%, and NAMPT is the rate-limiting enzyme for the recovery of NAD+ from its metabolic breakdown product, nicotinamide. In other words, implementing time-restricted eating and fasted

exercise will naturally increase your NAD+ levels even without taking any NAD+ supplements.

More Information

Clement also reviews the possibilities of using CRISPR technology for gene editing, so for additional information, please listen to the interview in its entirety, or read through the transcript. He also discusses how his laboratory is pushing the limits to minimize the transitional period from discovery to integration into clinical medicine.

> *"[Many] for-profit companies that have gone into the antiaging field … have one particular target, one arrow in their quiver, essentially, to aim at [antiaging].*
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> *Most … get locked into spending the next four or five years working on a particular antiaging pathway that may or may not turn out to be all that important, whereas as a nonprofit and supported by donors who really want to foster antiaging, I can say that we're looking at dozens of different completely independent pathways for antiaging,"* Clement says.
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> *"I've read between 18,000 and 20,000 scientific papers on aging. I've made long notes about the things that were working on model organisms, like flies and mice, for example. In many cases, we know that these same things should work in humans, but the molecules or the techniques used are generic drugs or compounds that you can't patent for various reasons …*
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> *Therefore, there's just not a financial incentive for a venture capital company to fund someone researching metformin, let's say, and rapamycin, both of which are generic drugs, specifically for antiaging.*
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> *What you see is the venture capital companies are putting money into companies that want to create novel compounds that mimic compounds we already know about.*

But no one's really studied or optimized those compounds … and because anybody can knock that off, you might see a pharma company trying to create a synthetic molecule that takes attributes of those and has a particular molecular benefit similar to what they do.

But my parents, my elderly friends, they don't have 10 years to wait. And then, often, these drugs are really powerful. For a lot of people, they aren't appropriate anyway. The natural compound or the generic drug that we already knew about would have probably been a better choice.

What we want to do is take a lot of these compounds that are already proven to work in other organisms, try them on humans, and then if they do seem to work, then we go through a process of optimizing them.

If they don't work, we just simply drop it and move on. Because no one's counting on us turning this particular thing into a product, so we don't have that weight over us that somehow the one and only thing that we chose now has to be [profitable] …

Everything that we've talked about today is a result of decades' worth of very intense research by hundreds and hundreds of scientists that are focused on antiaging and who are not specifically trying to make a profit from a single molecule or cell line or therapy, but merely doing the hard work of telling us what seems to work and what doesn't.

And then testing those in model organisms, from C. elegans, worms, drosophila, fruit flies and rodents, like mice and rats.

Much of this is already known that we can rapidly, I think, qualify these things in humans using these clinical trials and know, 'OK. This is worth spending more time on because it has profound antiaging effects or it helps one particular morbidity pathology.'"

It was to this end, also, that Clement wrote "**The Switch: Ignite Your Metabolism With Intermittent Fasting, Protein Cycling, and Keto**," which I highly recommend adding to your library. Reading through it, and implementing the strategies covered in this book can go a long way toward warding off age-related diseases and optimizing your longevity.