

Carty foresees a day when AMI is the standard approach for amputations. “This technique could allow patients who’ve undergone limb loss to recapture a degree of ‘wholeness’ that is usually lost forever for amputees,” he says. “This represents a way to get at least some of that—and maybe a lot of that—back.” ~ERIN O'DONNELL

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Anti-Aging Approaches

DECADES of research have shown that calorie restriction extends lifespan and delays morbidity in many small, short-lived species: yeast, spiders, and various fish and rodents. In humans, though, the benefits of calorie restriction are still unproven, and prob-

ably less straightforward. And *how* calorie restriction slows the aging process is still not well understood. “The interesting thing about calorie restriction is that we used to think the body was in some way slowing down, maybe in the number of heartbeats or production of free radicals,” says professor of genetics David Sinclair. “But it turns out that’s wrong...When we’re calorie restricting, what we’re really doing is telling the body that now is not the time to go forth and multiply. It’s time to conserve your resources, repair things better, fight free radicals, and repair broken DNA.”

Sinclair believes that a compound found in all living cells, nicotinamide adenine dinucleotide (NAD), could be used to mimic these effects in humans without the starvation or decreased reproductive capacity associated with calorie restriction; his human trials of a therapy that could increase NAD levels are due to begin this month. Meanwhile, a similar compound is already being marketed as a supplement by a health start-up with several distinguished scientists (including three Harvard faculty members) on its advisory board—even though there’s still no evidence that the substance works.

Sinclair’s approach is based on a broad view that links diseases of age such as cancer, diabetes, Alzheimer’s, and heart failure to common cellular processes. His lab aims to understand these processes and then use that understanding to develop medical therapies.

Underlying the wide-ranging benefits of calorie restriction, Sinclair explains, are sirtuins—a group of seven genes that appear to be very important in regulating the aging process. “These longevity-gene pathways are turned on by changes in lifestyle” such as exercise and calorie restriction, he says. They “control a variety of protective processes—there’s hundreds of things that they do, and we still don’t know everything. But they protect the chromosomes, they protect stem cells from being lost, they protect cells from senescing.” Sirtuins can be activated by a lack of amino acids or of sugar, or through an increase in NAD. (The compound’s level in the body declines with age.)

Earlier this year, research from Sinclair’s lab showed that feeding mice nicotinamide



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mononucleotide (NMN)—a related, precursor compound that the body converts into NAD—may slow aging in the animals, mimicking the effects of calorie restriction. “We get the same effects as exercise or dieting,” he says. “The mice are leaner, have more energy. They can run further on a treadmill.” That research continues, and is poised to be tested in humans: the first stage of the trials of NMN that he was preparing to begin in August at a

Human trials of an anti-aging therapy will begin this month.

Harvard-affiliated hospital will test for NAD increases in the blood; after that, he plans to study NMN’s efficacy in treating diseases. Sinclair has been taking the compound himself for about a year. He’s reticent about that, to avoid sounding like a “kook,” but claims his lipid profile has improved dramatically and he feels generally less fatigued—though he admits this is not scientific.

There is a cautionary note to sound, says Jeffrey Flier, Walker professor of medicine and former dean of Harvard Medical School (HMS). The NAD precursor already on the market as a dietary supplement, nicotinamide riboside (NR), is sold by New York-based Elysium Health, founded by MIT biologist Leonard Guarente, Ph.D. ’79, who played a central role in establishing the link between sirtuins and aging, and was

Sinclair’s doctoral adviser. The company doesn’t make any specific claims about aging prevention (legally, it can’t); instead, it promotes its product as “the one daily supplement your cells need.” Flier has criticized the company for using the names of the highly credentialed scientists on its advisory board (featured prominently on its website) to market an unproven product: “Elysium is selling pills [without] evidence that they actually work in humans at all,” he says, echoing the strongly worded *Boston Globe* op-ed he wrote earlier this year condemning the company’s marketing scheme.

Sinclair, who co-directs the Glenn Center for the Biology of Aging at HMS, is not linked to Elysium—his clinical trials go squarely down the traditional medical route, rather than through the loosely regulated supplement industry. “That’s the contrast,” he says. “I’m taking a pharmaceutical approach, FDA approval.” Still, whatever animal research portends about the potential of NAD (and however alluring the promise of a cure for aging), the history of pharmaceutical development suggests it’s much too soon to expect any benefits for humans. Often “molecules may be helpful to animals in a limited set of studies, but then are not shown to be helpful in humans,” Flier warns. “There are *many, many, many* examples of that.” ~MARINA BOLOTNIKOVA

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