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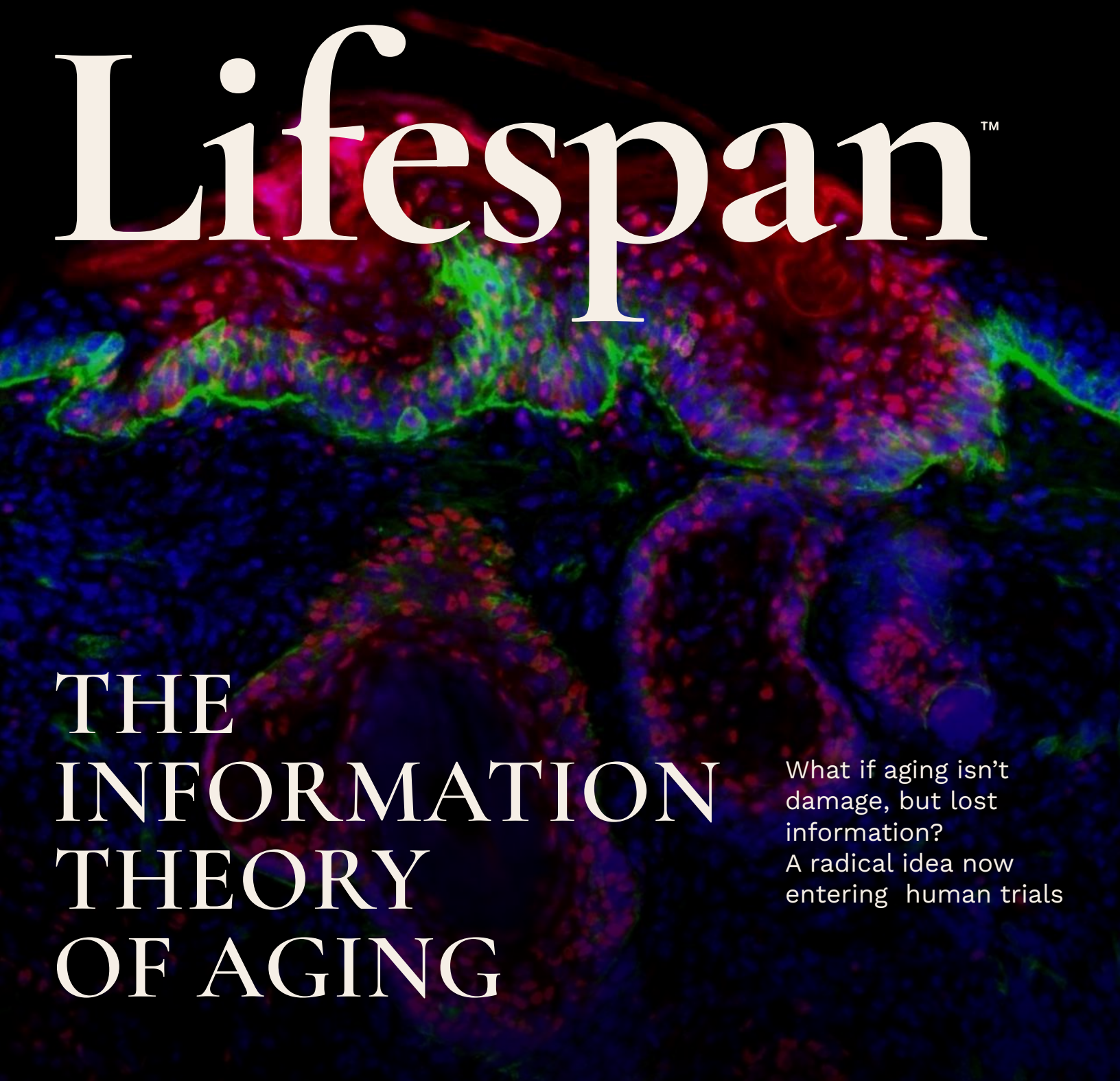
Lifespan™



THE INFORMATION THEORY OF AGING

What if aging isn't damage, but lost information? A radical idea now entering human trials

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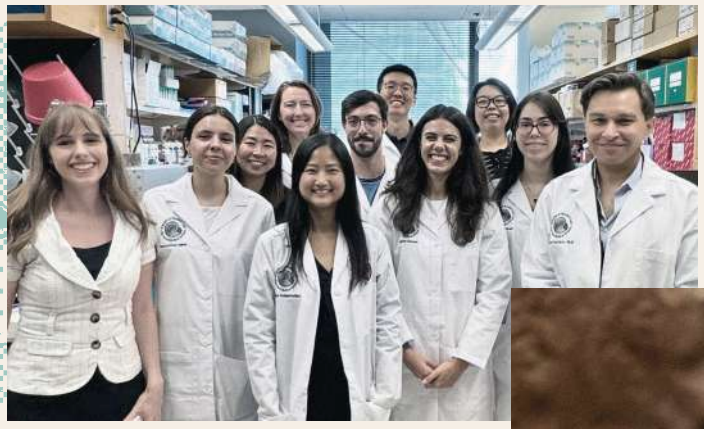
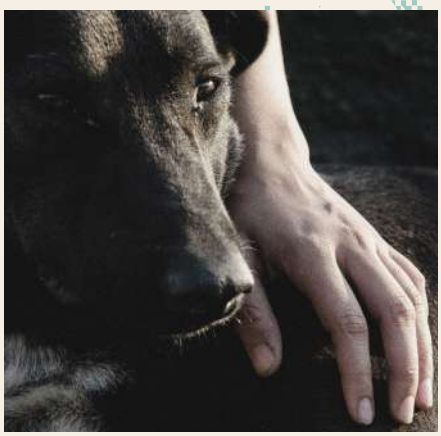
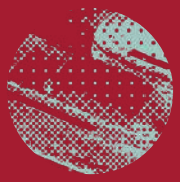
Lifespan Magazine's print and downloadable editions are designed in a traditional magazine format. Throughout the issue, photography and illustrations extend across two-page spreads to create a more immersive reading experience. We encourage reading it in two-page "magazine spread" mode whenever possible.

COVER IMAGE: YUCHEN GAO, PHD, SINCLAIR LABORATORY
MAGAZINE DESIGN: RYAN MURPHY, HEBA DAGHISTANI

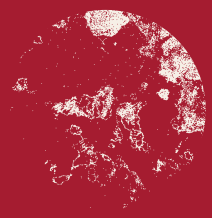
Table of Contents

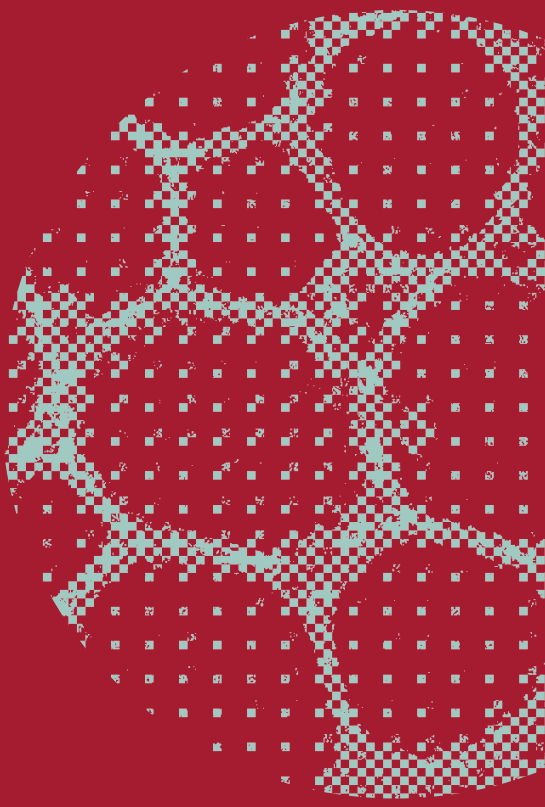


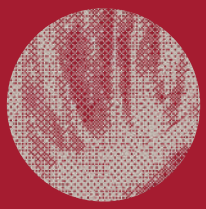




WELCOME TO LIFESPAN: A FOUNDING EDITORIAL







This is a magazine created for you, the reader. Thank you for subscribing. Together, we are going to do amazing things.

If you love life and want it to last as long as possible. If you want to stay healthy, sharp, and capable for decades to come. If you want to live fully without becoming a burden on the people you love. Or if you simply want to perform at your highest level for as long as possible, then this magazine is for you.

BY DAVID A. SINCLAIR, AO, PHD

Over the years, I've listened carefully to you, my audience, people who are curious, optimistic, and determined to take control of their health and their future. *Lifespan* is my answer to those conversations.

Some of you may have read *Lifespan*, a book I co-wrote in 2019. Others may have listened to the *Lifespan* show. Today we're launching a new endeavor, *Lifespan Magazine*. Across all these efforts, my goal is the same: I want to create opportunities for learning where the science is checked, the claims are sourced, and the advice is judged by whether it is credible, useful, and grounded in real data. However we reach you, we're glad you're here. And if you want to stay up-to-date with all our resources, it's my hope that you'll consider joining the Lifespan Community. By doing so you'll be directly supporting medical research.

My promise is simple:

1. Provide only evidence-based information on science and health

2. Give practical information that helps you live a longer, healthier life

3. Support medical research

4. Build the largest global longevity community that can rebuild healthcare from the ground up

This isn't another wellness publication chasing trends. It is part of an ecosystem built for members around science, transparency, and action.

And the timing could not be better.

Lifespan Magazine is launching at a moment when longevity, prevention, and healthy aging have moved from the margins of science into the mainstream. What was once a niche academic field is now one of the most exciting frontiers in medicine, biotechnology, and human potential.

The next decades will transform how we think about aging and disease.

This magazine exists to help you understand that transformation, and to help you benefit from it.

Welcome to *Lifespan*.

Why launch now?

Too much of the public conversation about health is now filtered through an influencer wellness industry that is often uncredentialed, poorly sourced, conflicted, and detached from evidence.

Recent research describes a digital environment in which health and nutrition content is heavily shaped by marketing and influencers. Research has found that 44.8% of nutrition information posted by popular Instagram accounts contained inaccuracies.[1] Consumers want better answers about what to take, how to exercise, what to eat, and how to live their longest, best, healthiest lives. What is missing is a publication that treats the reader with respect.

There is a section of society that is tired of all the clickbait from newspapers and TV. They want:

1. Real facts, not fads

2. Well-researched articles, written by scientists

3. Evidence-based recommendations, not slogans

4. More medical research, not more billionaires with racecars

5. Making medical innovations accessible to everyone

If any of this resonates with you, then we hope you'll join us. We're creating a place where curious people can learn together, ask hard questions, and act on the best available evidence.

A field moving from fringe to mainstream

The global wellness economy reached $6.8 trillion in 2024 and is projected to reach $9.8 trillion by 2029.[2] At the same time, scientific and commercial interest in aging biology has accelerated, from standalone companies to broader activity across pharma, artificial intelligence, genomics, and precision health.

One clear sign of that shift is the emergence of well-funded companies built around aging biology. Altos Labs has focused on cellular rejuvenation and restoration, while Retro Biosciences has positioned itself around extending healthy lifespan and preventing or reversing age-related disease. This is no longer a fringe conversation. It is now part of the core strategy of a growing set of serious research organizations and investors.

The future is consumer biotech. GLP-1 drugs changed the psychology of medicine and of consumers. These drugs began in diabetes, expanded into obesity, then showed broader relevance across cardiovascular and metabolic disease, and, more recently, aging. A 2025 editorial in *Nature Biotechnology* explored the question of whether GLP-1s might be the first longevity drugs.[3] It's clear that they work across multiple systems, even having a beneficial impact in substance use disorders.[4]

Whether or not GLP-1s ultimately prove to be longevity therapeutics, they have already accomplished something consequential: they have made the notion of interventions that slow aspects of aging both credible and imaginable to a broad public. This may well foreshadow the path by which the first true longevity therapies reach the mainstream.

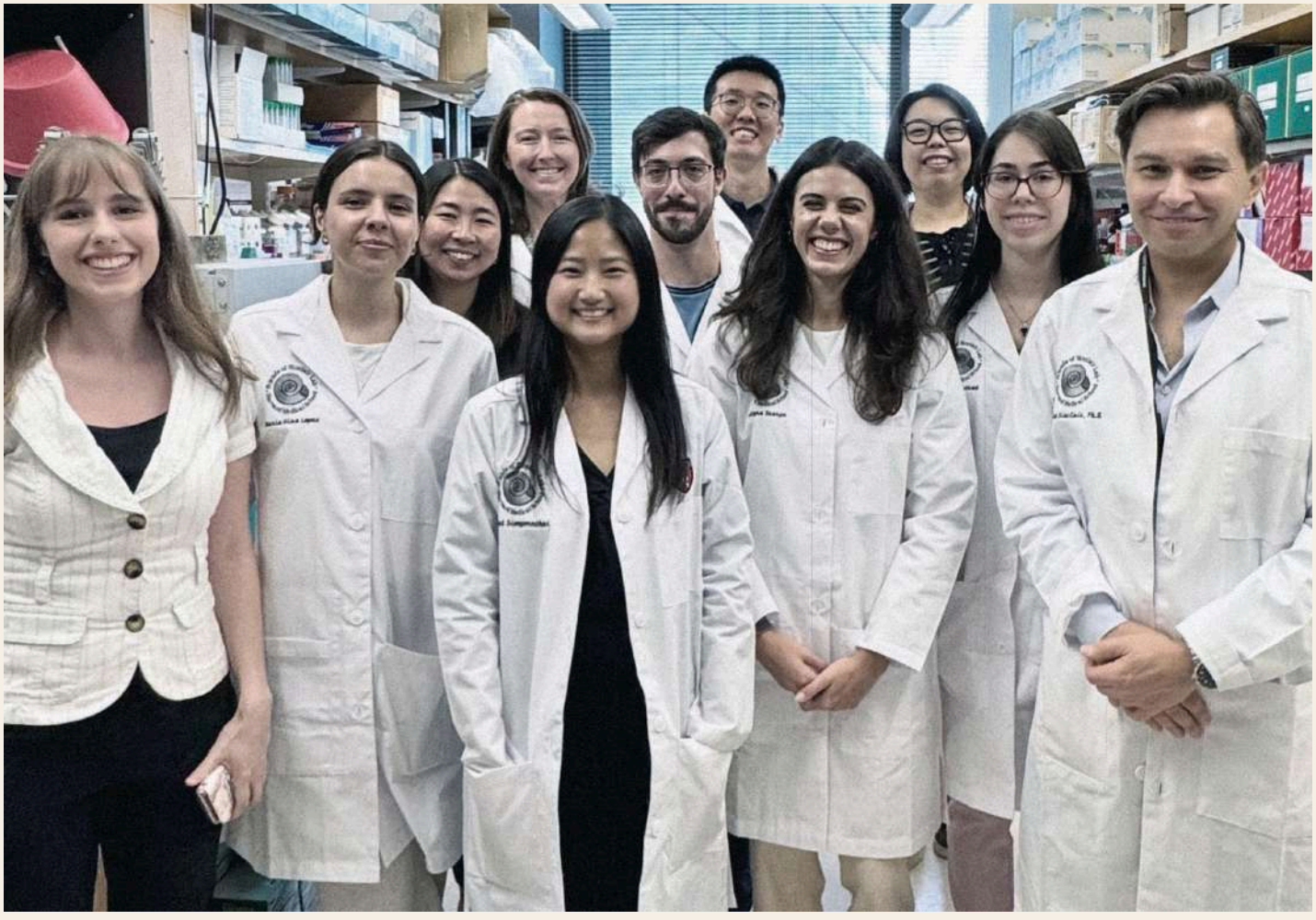


IMAGE SOURCE: DR. DAVID A. SINCLAIR, AO, PHD

The convergence that is changing medicine

Aging remains the single greatest risk factor for most chronic diseases. There are others, of course. Smoking is dangerous and rightly carries that reputation. But scale matters. Smoking increases the risk of many cancers by roughly 2 to 3 times. Aging, between about 40 and 75, increases cancer risk by approximately 30 to 40 times. If medicine is serious about reducing the burden of disease, it must ultimately confront the biology of aging.

This is not only a scientific problem. It is an economic one. In 2021, Dr. Andrew Scott, Dr. Martin Ellison, and I published *The Economic Value of Targeting Aging* in the scientific journal *Nature Aging*.[5] We estimated that slowing aging enough to extend life expectancy by just one year would generate approximately $38 trillion in societal value. Extending healthy lifespan by ten years would yield about $367 trillion. These figures help explain why longevity is no longer a niche conversation. It is emerging as a central priority for public health, biotechnology, and the global economy.

What we are now seeing is the convergence of molecular biology, genomics, AI, and biotechnology. This convergence is not theoretical. It is already reshaping how disease is measured, how therapies are developed, and how health is monitored.

On the drug discovery side, a clear example is AlphaFold,[6] which transformed structural biology by making protein prediction dramatically faster and scalable. In my own laboratory, AI is now used to search vast chemical spaces for molecules that may slow or reverse aspects of aging. It can analyze microscopy images and estimate the biological age of cells in seconds. Increasingly, AI is beginning to function as what might be called an agentic scientist: a system that amplifies the reach of good scientists. As Dr. Nicholas Galakatos, Global Head of Blackstone Life Sciences, has noted, drug development is hard and expensive. That is precisely why better tools for choosing targets, screening molecules, and interpreting results matter so much.

The same logic is reshaping personalized medicine. The clinical frontier is no longer just the genome. It is the genome, the epigenome, blood biomarkers, sleep, glucose dynamics, activity, medications, environment, and how these change over time. Wearables, blood tests, and home diagnostics are important because they transform health from an occasional snapshot into something closer to continuous sensing. AI makes that stream interpretable. Increasingly, these data can help forecast disease risk and identify interventions before symptoms begin.[7,8] That was an argument I made in the *Lifespan* book: biology would become measurable, trackable, and ultimately predictable.

This is the convergent environment in which we now find ourselves. It sets us up for an era of extraordinary medical progress, if we can guide it with evidence and judgment.

"*Lifespan* will be more than a magazine. A serious publication in this field should do more than track papers, companies, and policy."

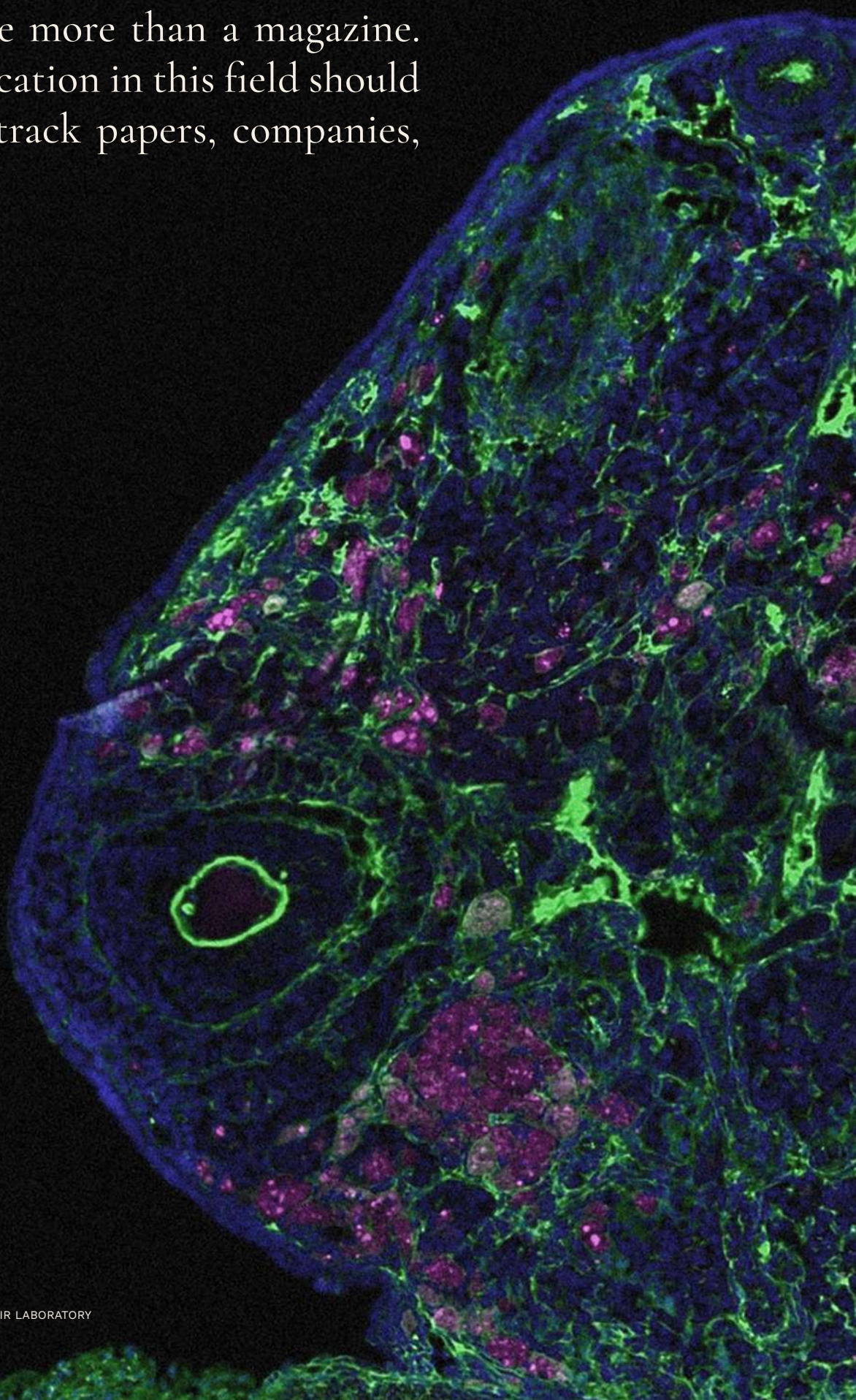
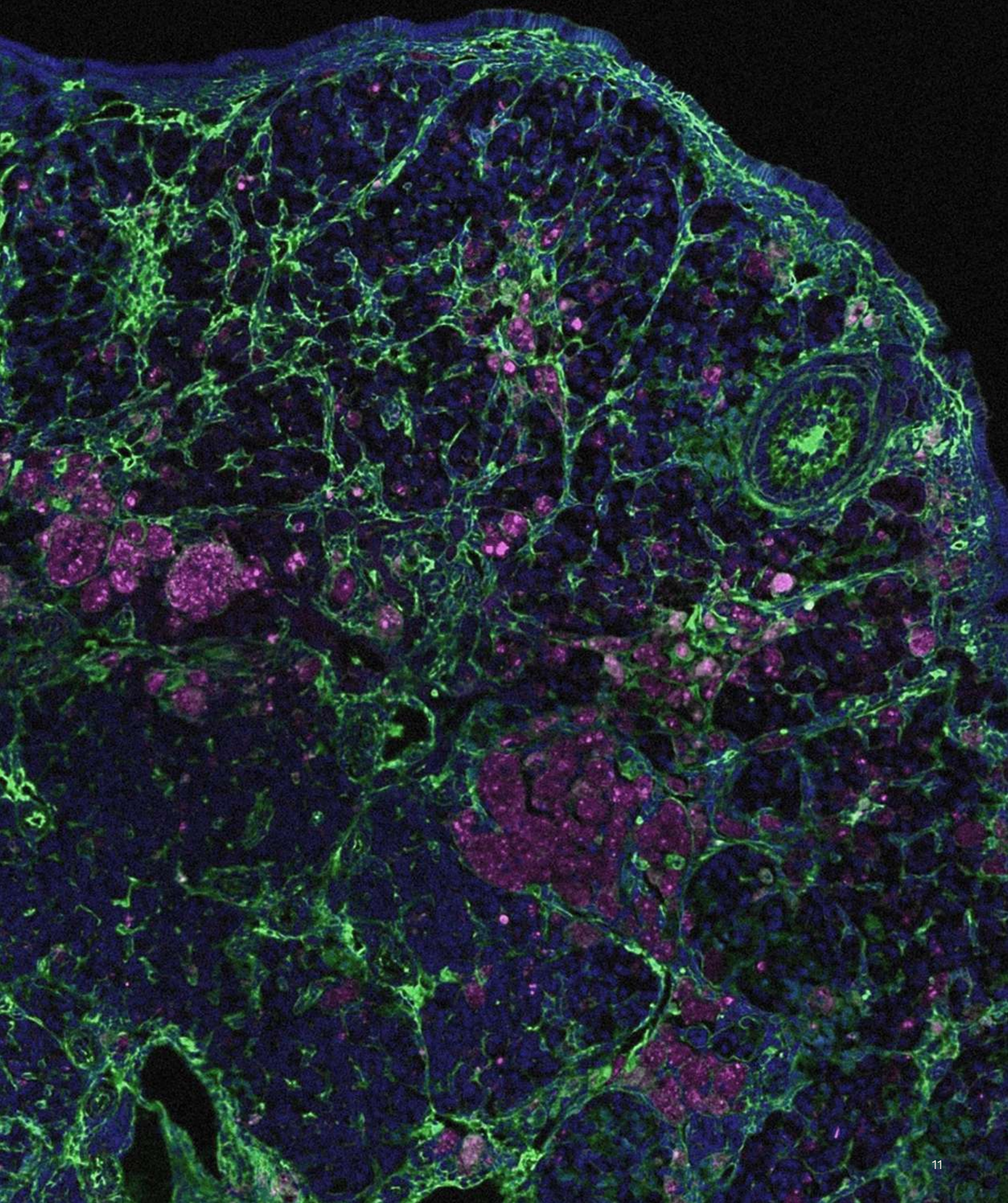


IMAGE SOURCE: MARIA VINA LOPEZ, SINCLAIR LABORATORY



The new tools driving longevity science

Genomics is undergoing a parallel transformation. The first human genome cost billions of dollars to complete. The field is now pushing toward the $100 genome. Once sequencing gets that cheap, the bottleneck changes. The expensive part is no longer producing the sequence. It is organizing, integrating, and interpreting biological data at scale.[9]

Oxford Nanopore is a company which has been foundational in making genetic sequencing portable and real-time. The field it helped build is now moving toward commoditized sequencing hardware and much greater strategic value in unique datasets and interpretation. That shift echoes what Larry Ellison has argued from the AI side: the durable value may not be the machine generating the data, or even the model processing it, but the high-value private data itself. In biology, that principle may be even more important than in software because the next major advances are likely to come from datasets that are longitudinal, clinically rich, and hard to replicate.[10]

More detailed and specific sequencing techniques are now providing more data than ever before. Single-cell sequencing allows scientists to track changes in individual cells rather than averaging across many cells, revealing which cell states are driving disease and where resistance or vulnerability sit. In practical terms, single-cell genomics is changing how we detect disease, validate targets, stratify patients, and design medicines.[11,12]

Together, these developments show that the tools for doing science are improving faster than ever, and that the central challenge is no longer access to data, but knowing how to use it wisely.

Longevity medicines come of age

Taken together, these trends point in the same direction. Aging itself is becoming a direct target for medicine. It's no secret that my own work has focused on aging, but therapies developed with aging in mind can also be used to treat specific diseases. We are now entering an era in which age-focused interventions are moving from theory into human trials.

One example is ER-100, a gene therapy developed by Life Biosciences, a company I founded and chair. ER-100 is designed to restore a more youthful epigenome to diseased cells in the eye, with the aim of helping them regain lost function. ER-100 has been approved by the FDA to move to clinical trials for people with certain optic nerve disorders.[13] If you're interested in the details, an article later in this issue takes a deeper dive. Here, I mention it for a simpler reason: it illustrates how quickly the field is moving from understanding aging to attempting to reverse aspects of it in people.

Lifespan Magazine

A serious publication in this field should do more than track papers, companies, and policy. It should help build a public that can distinguish evidence from exaggeration, understand what is actionable today, and support the scientific work that remains to be done. This is the goal of *Lifespan* Magazine.

The field has moved beyond the point where it can be dismissed as fringe, but it has not yet reached the point where confidence should outrun evidence. Longevity is emerging as a legitimate scientific, medical, and economic domain. The tools are improving. The data is improving. Investment is increasing. Measurement is becoming more precise.

But progress brings a new obligation: standards. Readers need a source that can clearly explain what is credible, what is speculative, what is practical now, and what is worth supporting.

That is precisely why a publication like this should exist.

Thank you for joining us.

Be well,

David

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THE SLIME OF YOUTH: WHAT NAKED MOLE-RATS TEACH US ABOUT AGING

BY ADIV JOHNSON, PHD

IMAGE SOURCE: MIDJOURNEY

Dr. Vera Gorbunova and naked mole-rats

While most aging researchers study mice or human cells, Dr. Vera Gorbunova and her husband Dr. Andrei Seluanov built their careers studying – and mixing – the genes of whales, beavers, and perhaps the strangest animal in biology – the naked mole-rat. The naked mole-rat is a heavily wrinkled rodent that can barely see and lives in dark, underground tunnels. The most spectacular thing about these animals is that they can live for around 40 years and almost never get cancer.

This lifespan for such a small rodent is truly extraordinary. To give you a sense of just how unique this is, the common lab mouse used in scientific research has a maximum lifespan of three years in captivity. In comparison, the naked mole-rat can live more than 10 times as long! This amazingly long life starts to approach what is typically seen for some larger primates, including gorillas. Generally speaking, smaller animals don't live as long as larger animals. This is why many exceptionally long-lived organisms – like giant tortoises, bowhead whales, and Greenland sharks – are fairly large. Naked mole-rats stand out as living a really long time despite being small rodents.

Getting back to Dr. Gorbunova's lab at the University of Rochester, there are cages of naked mole-rats that sit under dim red light. The reason for this setup is to mimic the darkness of their underground tunnels in the wild. The animals scurry through the enclosure in constant motion, living in colonies that look more like those of ants or bees than typical mammals. Naked mole-rats are one of the few mammals that are truly eusocial. Each colony revolves around a single queen, recognizable by the large hump along her back, who gives birth to all the pups while the rest of the colony serves and protects her. Naked mole-rat queens maintain the astonishing ability to reproduce even into old age in their thirties.

Super hyaluronic acid, slimy cells, cancer, and aging

Then came the discovery that made headlines.[1] Dr. Gorbunova had noticed that cells from the naked mole-rat growing in the dish were extremely slimy and, like all good scientists, decided to investigate. In 2013, Dr. Gorbunova and her colleagues reported in the scientific journal *Nature* that naked mole-rats produce enormous quantities of an unusually long form of hyaluronic acid (often abbreviated as HA), a sugar polymer that is more than five times larger than the version found in mice or humans. It's also much lengthier and, according to Dr. Gorbunova, the hyaluronic acid "secreted by naked mole-rat fibroblasts is 6X longer than HA secreted by human fibroblasts." This ultra-high molecular weight hyaluronic acid accumulates throughout naked mole-rat tissues and appears to stop cells from becoming cancerous. When the molecule was experimentally removed, naked mole-rat cells suddenly became susceptible to tumors. The finding suggested that the same slippery molecule best known from skincare products may be one of the biological tricks that helps these animals live extraordinarily long lives with almost no cancer.

Why would these adorable, highly wrinkled animals have so much of this large version of hyaluronic acid? To understand this, we need to step into the environment of the naked mole-rats. In their natural setting, they live in dark, small tunnels under arid grasslands and savannas in Africa. A typical naked mole-rat tunnel will be around 1.2 to 2 inches in diameter and contain dozens to hundreds of animals. While many humans would find

this incredibly claustrophobic and terrifying, the reality is that naked mole-rats need to be able to squeeze through these narrow tunnels and around other animals. The large amount of hyaluronic acid produced by these animals contributes to their high skin elasticity, meaning that their skin is not only super stretchable but also returns to its original form afterwards. Skin elasticity is something that declines with human aging and many supplements or skincare routines are focused on improving this.

In 2023, Dr. Gorbunova published another hit *Nature* paper,[2] this time showing that hyaluronic acid also plays an incredibly important role in the aging process. To test this, they genetically altered mice so that they produce the uniquely large version of hyaluronic acid that naked mole-rats produce. The results were simply astounding and clearly showed that this compound can affect the aging process in mice. Not only was there less inflammation in the tissues of these animals, but they were protected against oxidative stress, which is something that can directly damage DNA. These animals also lived significantly longer. Average lifespan was increased by 4.4% and maximum lifespan was boosted by 12.2%. These mice were also much less likely to develop cancer. For elderly control mice that didn't produce this special hyaluronic acid, 83% of animals developed cancer. For the very old genetically tweaked mice that did produce this naked mole-rat molecule, the incidence of cancer dropped to 49%.

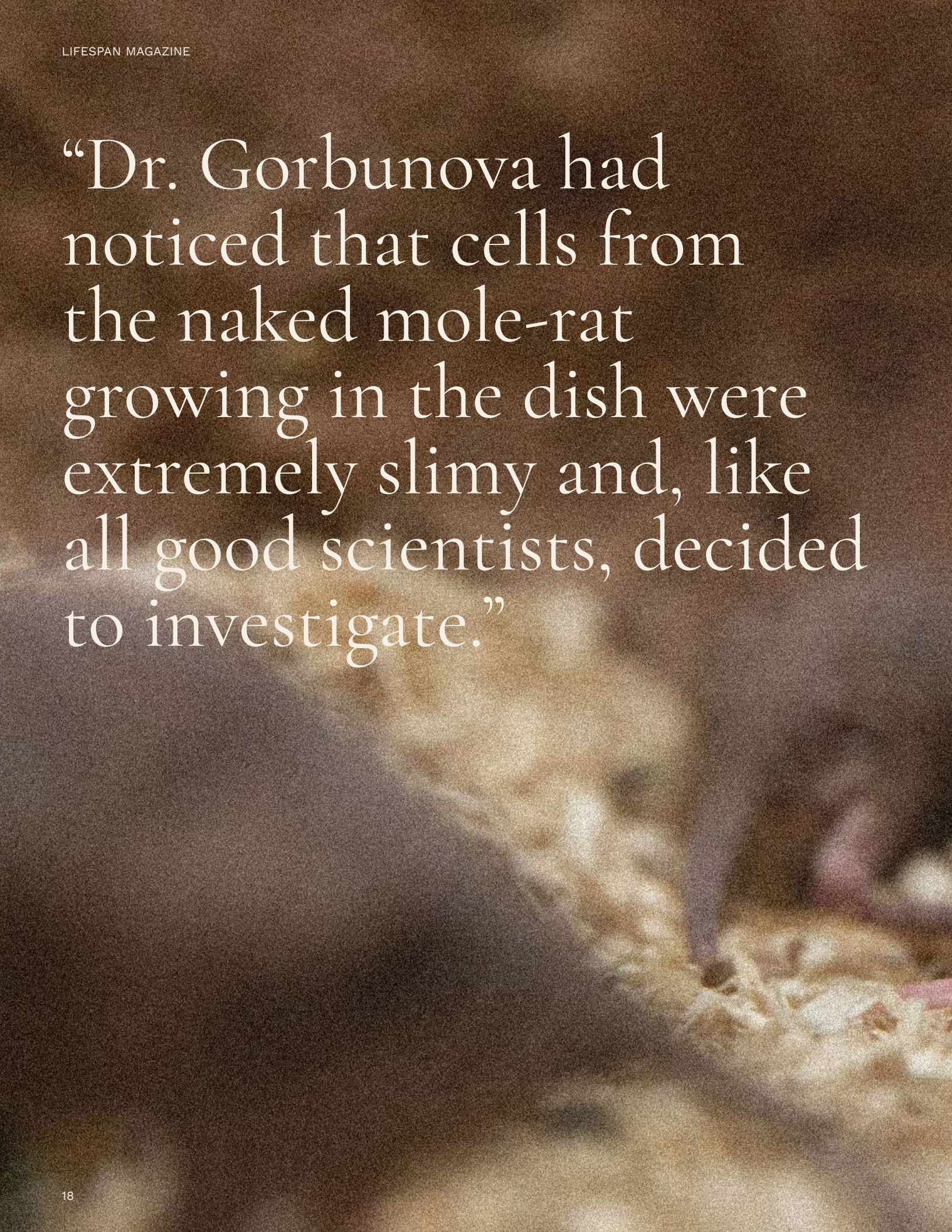
The scientists in this study also tried to give these mice skin tumors by treating them with toxic chemicals. Once again, this unique form of hyaluronic acid was protective and these special mice were much less likely to develop cancer. As if all of this weren't amazing enough already, mice producing the naked mole-rat version of hyaluronic acid were less frail, had better grip strength, and showed superior motor coordination. A bone marker of mechanical strength was also improved in older female mice. This is interesting because osteoporosis – the loss of bone mass – is something that older women are very much at risk of. Summarizing the key results from the study, Dr. Gorbunova shared that the naked mole-rat version of hyaluronic acid "has anti-inflammatory properties, promotes stem cell maintenance, and limits cancer metastasis."

IMAGE SOURCE: EVDOHA VIA ADOBE STOCK

Hyaluronic acid's origin story

Like many things in science, hyaluronic acid has a pretty cool origin story. One hot summer in the 1930s, a scientist at Columbia University named Dr. Karl Meyer was studying the clear gel inside a cow's eye. This gel is called vitreous humor and exists between the lens (which focuses light) and the retina (which takes light and converts it into meaningful signals within the brain). He found a strange, slippery substance that seemed to hold water better than almost anything known in biology. Meyer named it hyaluronic acid and, nearly a century later, that same molecule has become a widely used and well-known compound.

Meyer combined the Greek word hyalos, meaning glass or vitreous, with uronic acid, a type of sugar acid found in the molecule. The result was hyaluronic acid, referencing uronic acid from the



“Dr. Gorbunova had noticed that cells from the naked mole-rat growing in the dish were extremely slimy and, like all good scientists, decided to investigate.”

IMAGE SOURCE: SMITHSONIAN INSTITUTION VIA UNSPLASH

glassy part of the eye. Another surprising part of the story is how long it took to understand what had been discovered. Meyer and his colleague first reported the substance in a 1934 paper in the Journal of Biological Chemistry titled "The Polysaccharide of the Vitreous Humor,"[3] but the full repeating chemical structure of the molecule was not worked out for nearly twenty years afterward.

At the time, scientists mostly thought of it as a strange "goo" molecule that helped make tissues slippery and viscous. Only decades later did researchers realize how widespread it was in the body, forming the hydrated scaffolding of skin, cartilage, connective tissue, and synovial fluid in joints.

Hyaluronic acid and human clinical trials

One of the more exciting developments recently is that hyaluronic acid is now being tested in controlled human clinical trials, the gold standard for testing whether or not something has a direct effect on health. Hyaluronic acid isn't just being tested as a filler, but as a systemic treatment for skin aging. In one clinical study published in the journal *Skin Research & Technology* in 2023,[4] 129 women were given hyaluronic acid in liquid form at a dose of 100 mg or 200 mg. After two to eight weeks, skin hydration was significantly improved among younger and older women. Skin tone started to improve after four to eight weeks and, after 12 weeks, the outermost layer of skin (known as the epidermis) had measurably thickened.

This isn't the only trial to report that hyaluronic acid can benefit human skin. In 2025, a group of researchers from the Czech Republic published an exciting paper in the journal *Scientific Reports*.[5] The researchers took 150 people and randomly assigned them into three different groups. The first group received 60 mg of hyaluronic acid, the second group got 120 mg of hyaluronic acid, and the third group received a placebo with no hyaluronic acid. The researchers looked at many different variables, such as skin hydration, thickness of the outermost skin layer, wrinkles, and skin stretchiness. After 12 weeks, hyaluronic acid broadly improved skin relative to the placebo control group. Skin hydration, elasticity, structure, and wrinkle depth (wrinkles typically get more prominent with age) were all enhanced.

While looking at individual clinical trials is definitely worthwhile, there's actually an even higher tier of evidence with a fancy name called a meta-analysis. What a meta-analysis does is take the results from many different clinical trials and combine them for a much larger, more impressive analysis. What this does is allow researchers to make more confident claims about the ability of a drug or supplement to have a certain effect on human health. In September of 2025, a meta-analysis was published that looked at seven different randomized clinical trials that all used oral hyaluronic acid.[6] The results of their meta-analysis confirmed that hyaluronic acid could significantly improve wrinkle depth, skin elasticity, and skin hydration.

Looking to the future

Taken together, these trials suggest something surprising: hyaluronic acid may not only work when applied locally to the skin but may also influence skin biology when taken orally. This might occur because fragments of hyaluronic acid are absorbed in the gut and trigger signaling pathways that stimulate the skin to produce more of its own hyaluronic acid and strengthen the skin barrier. While the improvements are modest, the idea that a simple sugar polymer already present in our bodies could measurably improve skin physiology in

controlled trials has made hyaluronic acid a closely watched molecule in both dermatology and longevity science.

The findings in animals are also extremely fascinating. In addition to the *Nature* study we already mentioned showing that mice expressing the naked mole-rat version of hyaluronic acid live longer, healthier lives, there's also evidence that a form of hyaluronic acid extends lifespan and stimulates antioxidant defenses in worms.[7] This is definitely a worthwhile molecule to monitor and there's no doubt that many more interesting studies are on the horizon for hyaluronic acid.

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WHEN CELLS FORGET: INSIDE THE INFORMATION THEORY OF AGING

BY KELLY RICH, MS, CGC, PHD

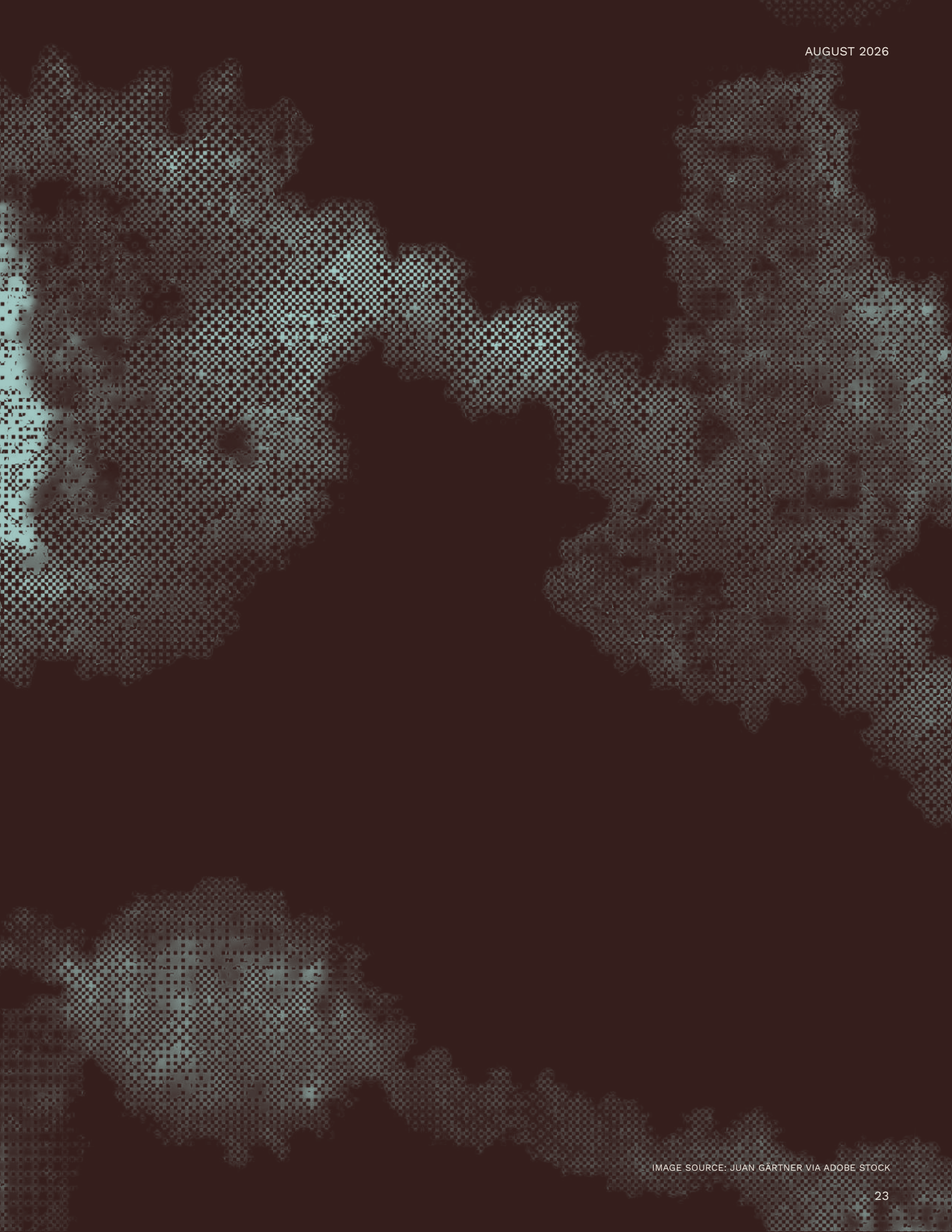


IMAGE SOURCE: JUAN GÄRTNER VIA ADOBE STOCK

"What if aging and age-related diseases – Alzheimer's disease, Type 2 diabetes, heart disease – are ultimately just manifestations of cells forgetting how to be young?"

A patient sits in the exam room, waiting to be seen by his doctor. His mind drifts, as it often does, to his family. He pictures his granddaughter's face – the freckles, the missing teeth, the bright smile. But when she lifts her hand to wave, it vanishes just as it leaves the center of his vision. He turns his head to find it, like searching with a flashlight whose beam has narrowed to a small circle. The living room where he sits is all missing pieces: no chair legs, a missing lamp, a door without a handle. Everything at once is both there and not there, present but just out of frame. He no longer trusts doorframes, curbs, or crowded sidewalks. The danger is not where he looks, it's where he can't. This is the grim reality of glaucoma. And it only gets worse.

Back in the room, the doctor arrives. She wants to talk about a new study the clinic is joining to treat patients with glaucoma, a first-in-human trial of a gene therapy called ER-100. The treatment, she says, would deliver three genes into his optic nerve, aiming to coax his cells to behave more like they did when he was young. She explains that the origins of this treatment are not related to glaucoma or even the eye at all, but basic research into why we age. This research has suggested that as we get older, cells can begin to "forget" their identity. In the eye, that means cells gradually lose the precise functions required to carry visual information to the brain. Some scientists now view diseases like glaucoma through this lens, less as a specific problem of the eye and more as what happens when cells in the optic nerve lose their identity. And in fact, this principle appears to apply more and more broadly across tissues and diseases.

What if aging and age-related diseases – Alzheimer's disease, Type 2 diabetes, heart disease – are ultimately just manifestations of cells forgetting how to be young?

Aging, reimagined as an information problem

ER-100 represents the first clinical test of a larger idea about aging itself, an idea called the Information Theory of Aging (ITOA). For ER-100 to make any sense, you have to accept a strange premise: cells carry memories. Cells remember who they should be, which genes to turn on and off, how to organize themselves into a tissue. These memories are written into patterns of gene expression, managed by a control system known as the epigenome. In glaucoma, as in many age-related diseases, those memories start to blur. Gene expression patterns become dysregulated, cellular identity weakens, and function declines.

The ITOA invites us to shift perspective. Rather than viewing the body simply as a collection of mechanical parts that wear out over time, we can see it as a dynamic system for storing, preserving, and interpreting biological information. Aging, in this framework, is the progressive loss of the cell's ability to read its own instructions correctly, and therefore to maintain its identity.

Aging biology is crowded with theories, but none has yet earned the status of a single, agreed-upon explanation. Most historical theories of aging are sorted into two broad categories: error-based and program-based. Debates in geroscience have long been framed as "damage vs. program." For much of the twentieth century, aging research was dominated by damage-accumulation theories: oxidative stress, free radicals, telomere shortening, and the promise of antioxidants shaped both the scientific conversation and, later, the consumer marketplace. The central idea was straightforward: cells accumulate molecular damage over time, and that damage eventually overwhelms repair systems. Yet the evidence we have – from comparative lifes-

pans, longevity mutations, and drugs that extend life – can almost always be interpreted in both directions. The same intervention may look like "less damage" in one framework and "turning down a quasi-programmed process" in another.[1–3]

Only more recently have theorists started to talk about aging as a problem of biological information – a gradual loss of the precise patterns of gene activity and communication that keep cells coordinated. ITOA grows out of this shift, asking not just how much damage there is, but what it does to the instructions that tell cells how to use their genes. Work from laboratories led by Dr. Leonard Guarente (Massachusetts Institute of Technology), Dr. Brian Kennedy (National University of Singapore), Dr. Shin-ichiro Imai (Washington University), and Dr. David Sinclair (Harvard Medical School) focused on chromatin regulation and the epigenome as central drivers of aging. Their findings point to a consistent story: changes in gene silencing and epigenetic regulation might be driving aging rather than simply reflecting it. This story was reinforced by later work in mammals showing age-related epigenetic alterations, shifts in chromatin structure, and DNA methylation patterns that reliably tracked with biological age. In other words, aging might have less to do with damage to the genome itself, and more to do with gradual errors in how that DNA is read.

Our genomes are the closest thing biology has to digital hardware. DNA is a long string of base pairs copied with remarkable accuracy from cell to cell and across generations. Your DNA sequence is essentially the same in a skin cell as in a neuron, in childhood and in old age. Yet those cells behave very differently, and they change in different ways over time. The difference lies not in the letters of the code, but in how that code is read.

By changing where chemical tags are added to DNA and the proteins that spool DNA, the epigenome decides which genes are switched on or off. Unlike the genome, it is largely dynamic. The epigenome is constantly being nudged by signals from inside and outside the cell – stress, diet, inflammation, DNA damage, and time. That flexibility is what lets cells adapt, but it also makes the system fragile. Over decades, epigenetic patterns can drift, tags end up in the wrong places, and the instructions are eventually so badly eroded that the cell forgets how to function.

From the perspective of the ITOA, genetic information itself is comparatively durable. You can even read the DNA of Neanderthals, a reminder that Jurassic Park's central idea (reading ancient DNA) has a real scientific basis, even if resurrecting dinosaurs does not. What fails with age is our cells' ability to read and interpret that information correctly. The theory proposes that aging is driven by the gradual loss and corruption of epigenetic information that tells cells how to use the genome, rather than by DNA mutations or other purely physical damage alone. Aging therefore is what happens when these information-maintenance systems can no longer keep gene expression programs on track, and cells become less coordinated, less resilient, and more vulnerable to disease.

From broken parts to broken instructions

The modern story of the ITOA began not with humans, monkeys, or even mice, but with microscopic yeast. Yeast are single-celled fungi – the same kind used to make bread and beer – and they've long been a workhorse of genetics because they grow fast and are easy to genetically manipulate.

In the mid-1990s, researchers at Massachusetts Institute of Technology, led by Dr. Leonard Guarente, sought to figure out why yeast cells age and how to slow this process down. The lab noticed a mutant

yeast strain that survived long periods of starvation and, even more surprising, lived about 30% longer than normal cells. The mutant, called *SIR4-24*, pointed the lab toward a group of genes named "silent information regulators" (*SIR*s). These genes were already known to keep certain stretches of the yeast genome transcriptionally "quiet," meaning those regions of DNA were tightly packed and their genes turned off. Now they seemed to be doing something else: determining how long the cells could live.

Zoom in on one of these silent information regulators, Sir2. In young cells, Sir2 keeps certain "sex" genes quiet so that the cell stays clearly one sex or the other, rather than a mix of both. It also sits with Sir4 and other partners on tightly packed DNA, including a fragile stretch that tends to break and form extra DNA loops. These loops, called extrachromosomal ribosomal DNA circles (ERCs), build up in old yeast cells and contribute to their death.[4] Sir2 is the catalytic workhorse of this silencing complex: by chemically modifying the proteins that spool DNA, it keeps specific regions of the genome quiet and preserves the cell's identity. Cells with extra Sir2 form fewer circles and live longer in standard lab conditions while cells without Sir2 accumulate ERCs sooner and die earlier.[5]

Between 1994 and 1999, work from the Guarente lab uncovered a pattern: when DNA damage occurs, Sir2 and its partners are pulled away from their usual posts on silent chromatin and sent to breaks in the genome to help with repair. DNA in cells breaks all the time, even under normal conditions. In young cells, Sir2 typically returns to where it started once the damage is fixed, but the system is not perfect. Each time Sir2 moves away, regions of DNA it was keeping tightly wrapped can loosen, genes that should stay silent can turn on, and over many cycles of damage and repair Sir2 does not always find its way back. The DNA letters themselves remain mostly correct, what changes is how the cell reads them. Old yeast cells, with misplaced Sir2 and an abundance of ERCs, ultimately lose their former identity. Their function changes, they lose the ability to mate, and eventually die under the burden of extra DNA circles that soak up transcriptional machinery.

The Sir2 story drew attention because it is part of a conserved family of genes, the sirtuins, with close counterparts in humans. That meant these yeast experiments might be pointing to a deeper, more universal rule about how cells age.

The conceptual leap came when these pieces were put together. DNA breaks actively pull sirtuins off their normal jobs, eroding the epigenetic landscape a little each time. Over many repair cycles, that relocalization changes gene expression, chips away at cellular identity, and eventually drives aging. In this light, aging looks less like the simple buildup of unrepaired lesions and more like epigenetic side effects of the cell's own repair processes. The DNA sequence can remain largely intact, yet the instructions layered on top of it drift. That shift, from broken parts to broken instructions, is what eventually crystallized into the ITOA.

From yeast to mammals: when repair erodes identity

Mammalian genomes and biology are vastly more complex than yeast, though similarities exist. As in yeast, mammalian chromatin regulators such as sirtuins are recruited to DNA breaks. They leave their usual posts at promoters and silent regions to help with repair and, in the process, change gene expression.[6]

To test whether such shifts in epigenetic information could cause aging, rather than simply accompany it, researchers at Harvard Medical School created the ICE model ("ICE" for "Inducible Changes to the Epigenome").[7] In these mice, targeted, easy-to-repair DNA breaks were introduced throughout the genome without increasing the overall number of mutations beyond what normal mice experience. The result was striking. Animals developed accelerated epigenetic age, disrupted chromatin architecture, and functional signs of aging – physical frailty, organ decline – much earlier than expected. Their underlying DNA sequence remained intact, but their epigenetic patterns resembled those of much older animals. In other words, the yeast story holds in a mammal: repeated activation of the DNA repair machinery gradually rewires the epigenetic landscape, and that loss of epigenetic information is enough to drive an aging-like state.

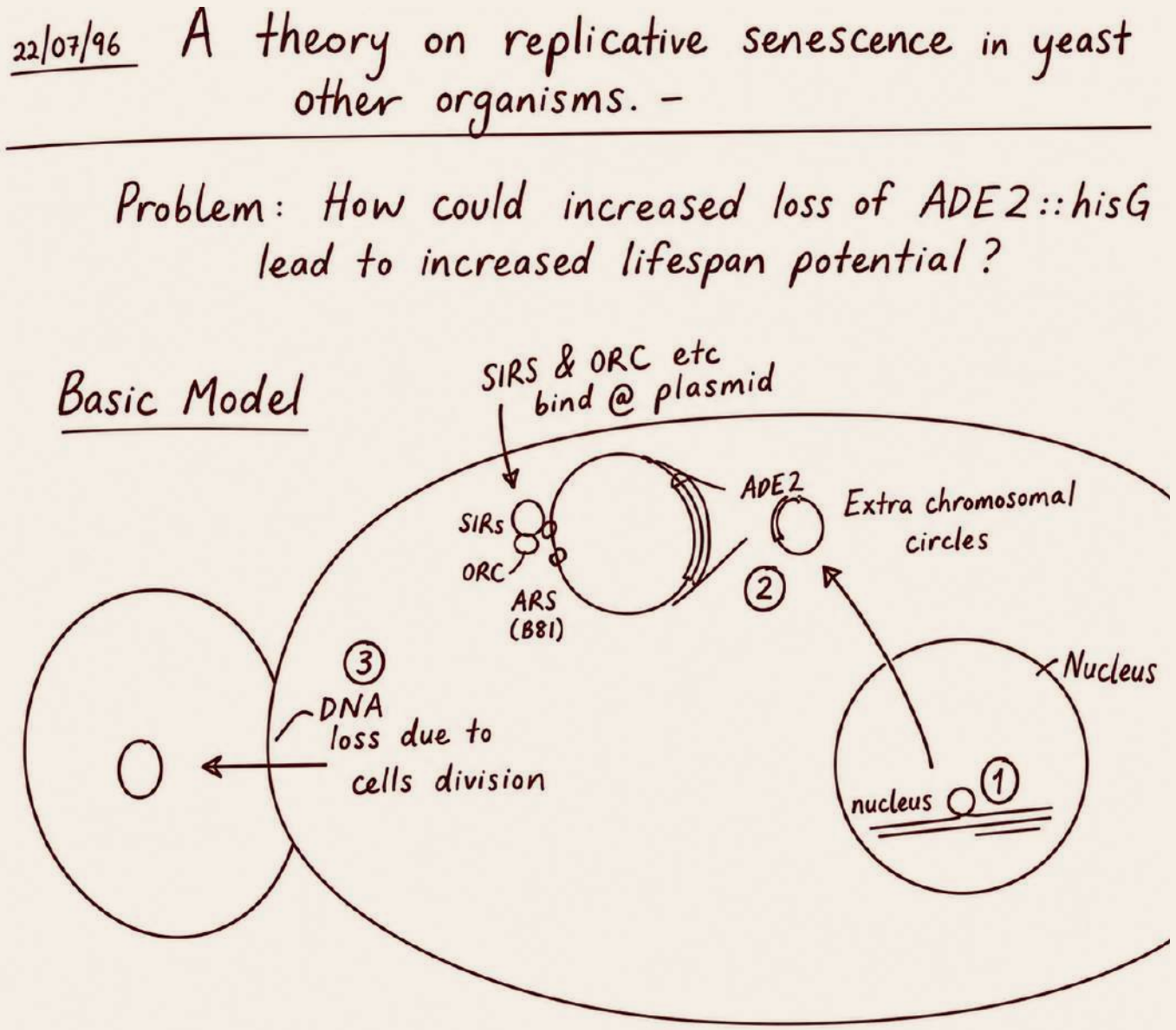
Epigenetic "noise" and Waddington's landscape

One way to visualize all of this is through a picture first drawn in the 1940s by the embryologist Dr. Conrad Waddington, a picture we now refer to as "Waddington's landscape". To represent a cell as it goes through epigenetic changes during embryonic development, he imagined a ball rolling down a sloped, hilly terrain. The landscape has peaks and valleys; each valley represents a different cell identity (e.g., skin, muscle, neuron) and the hills between them act as barriers. At the top of the hill is the ball – representing an early embryonic cell with no fixed identity. As the ball rolls downhill during development, it settles into one valley, maturing into a particular kind of cell and staying there.

In youth, the hills are tall and the valleys are deep. The boundaries between them are sharp enough that cells "know who they are." A skin cell doesn't suddenly act like a neuron because there is a high barrier between the skin valley and the neuron valley. This landscape is shaped by the epigenome, with its patterns of DNA methylation, histone modifications, and chromatin loops. These marks carve the valleys and build the hills, guiding cells into stable identities during embryonic development and keeping them there early in life.

With age, combined with toxins and radiation that causes DNA to break, the landscape changes. Early in adulthood, the hills start to erode, the valleys become shallower, and the borders between them soften. Epigenetic marks drift and accumulate noise, making the overall shape of the landscape less distinct. In midlife, there appears to be a more rapid shift in age and cells metaphorically begin to slide sideways into neighboring valleys. The result is a partial loss of cell identity: liver cells express genes they shouldn't, immune cells respond in the wrong way, and neurons don't quite behave like neurons. The aches, the memory loss, and the diseases begin. It's slow at first, but late in life, it's a catastrophic decline.

Waddington's landscape also helps frame how aging and age reversal might work. Shortly after fertilization, there is evidence that the epigenetic clock of embryos actually decreases until it reach-



es a "ground zero" of biological age.[8] This finding suggests that a rejuvenation event occurs naturally during the lifespan, thus providing a framework to consider age reversal. A similar process seems to help lizards, salamanders, and fish regrow tails and limbs, suggesting perhaps this technology will go beyond aging and into organ and tissue regeneration.

Even if we don't know exactly how epigenetic restoration works yet, we know that biology can rebuild a youthful epigenetic landscape. The ITOA predicts that similar principles could be understood and harnessed later in life.

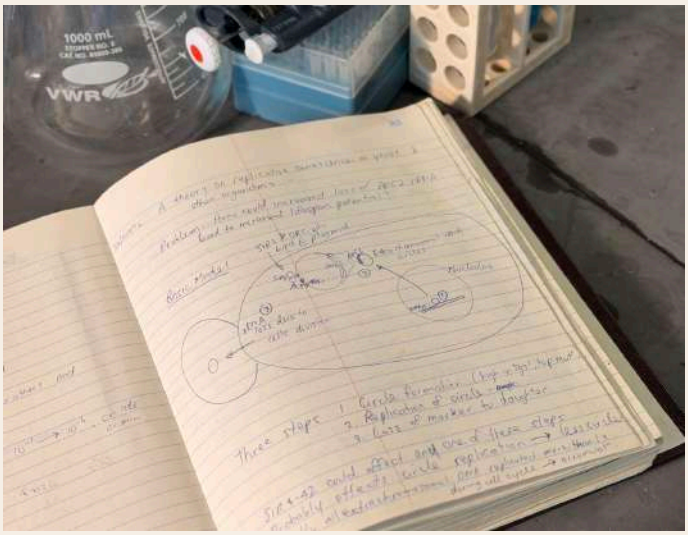


IMAGE SOURCE: DR. DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: MIDJOURNEY.

Shannon, backups, and the "youthful code"

If aging really is an information problem, it helps to ask how information survives in noisy systems at all. Mathematician Dr. Claude Shannon, a pioneer in Information Theory that led to the digital world we live in, tackled a version of this in the 1940s: how do you send a message through a channel that introduces random errors and still have it arrive intact? This was important for sending radio signals efficiently and for them to be understood by the receiver. His answer was that you don't eliminate errors, you correct them with a back-up. By building redundancy into the message and comparing what comes in against a clean reference, the receiver can spot where bits have been altered and reconstruct the original signal. Shannon formalized the idea that you can use a reference, sometimes framed as an "observer", to detect and correct errors.

The ITOA borrows this logic. If features of old cells can be restored to a youthful state, despite decades of noise and damage, then perhaps somewhere there may be a reference that defines "youth". Implicit in the ITOA is a suggestion that cells retain a latent backup of their youthful epigenetic state, a distributed record of which genes should be on or off, and how the epigenome should be arranged. That backup is not a single molecule but a web of molecular and structural cues specifying a youthful configuration of gene expression and chromatin architecture. Resetting it is complicated, involving thousands of genes and three-dimensional rearrangements of DNA, and we do not yet know where the reference copy resides, if it exists at all. Still, the fact that embryos reset their age and epigenetic restoration can push adult cells toward youth suggests that biology already knows how to recover that information. The challenge is to work out how embryos, lizards, and salamanders carry out this reset, and to harness those same pathways in a controlled way.

Reprogramming, with the volume turned down

If cells really do carry a backup of their youthful state, the obvious next question is whether we can access it in a safe way. The first clues that cells can be reprogrammed came from Dr. Shinya Yamanaka, who showed in 2006 that turning on four genes, *Oct4*, *Sox2*, *Klf4*, and *c-Myc* (OSKM), now called the Yamanaka factors, could "reprogram" mature cells back to a pluripotent, stem cell called an iPSC.[9]

That 2006 discovery ultimately won Yamanaka the Nobel Prize, but it also came with a problem: fully reprogrammed cells completely forget their identities. In animals, turning on OSKM can drive lethal tumors.[10] In early mouse experiments, animals died within days of continuous OSKM expression. It wasn't clear whether this was age reversal or simply a slow-motion catastrophe. And if reprogramming meant erasing cell identity, causing cancer or leading to death, how could it ever be used on patients?

For years, most scientists assumed that all four Yamanaka factors were required for reprogramming. Around 2009, several groups began exploring whether a subset of factors might induce a gentler form of reprogramming – enough to rejuvenate cells without erasing their identity, more of a restoration of the epigenetic landscape. After multiple combinations of embryonic genes and culture conditions failed to strike that balance, a surprising result emerged: dropping *c-Myc* and using just *Oct4*, *Sox2*, and *Klf4* (OSK) could decrease epigenetic age without making them stem cells or causing tumors.[11] In mice, brief OSK expression restored vision after optic nerve damage and reversed signs of aging in tissues such as muscle and kidney, including in ICE mice whose epigenome had been artificially aged by repeated DNA breaks.[7] In the last 10 years, OSK has since been applied in sever-

al contexts, showing benefit in reversing features of aging, injury and disease across experimental models.

When epigenetic restoration leaves the lab

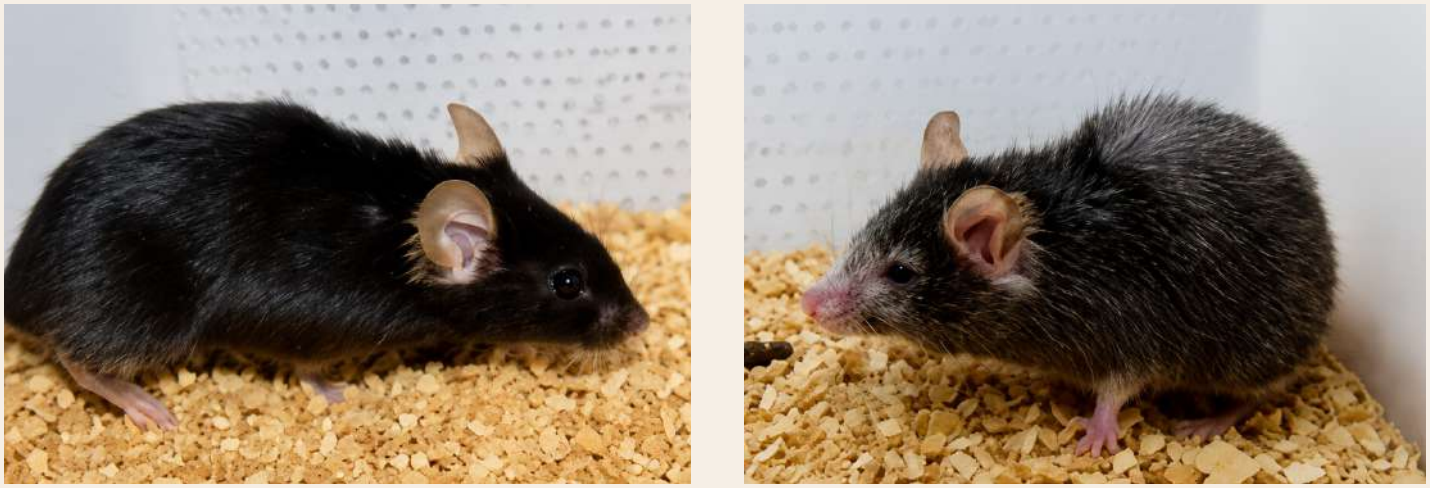
The harder challenge is translating a concept like this from the lab bench to the clinic, something only a tiny fraction of biological ideas ever achieve. To move beyond mice, researchers at Harvard Medical School, Massachusetts Eye and Ear Institute, and Life Biosciences used gene therapy to deliver OSK to retinal ganglion cells in non-human primates with optic-nerve injury and glaucoma-like damage. Treated animals showed measurable improvements in visual function, and their optic nerves exhibited DNA-methylation patterns that shifted toward those of younger monkeys. Importantly, in these early studies, the cells retained their identity as retinal neurons and no obvious safety signals emerged over the observation period, although longer and larger studies will be needed to rule out late effects and rare events.

Those results set the stage for ER-100, which has now received FDA approval for Phase I trials in people with glaucoma and non-arteritic anterior ischemic optic neuropathy (NAION), a condition caused by an acute reduction in blood flow to the optic nerve. These initial trials will test safety and dosing, and it remains to be seen how much functional recovery they will deliver. Even so, they represent something new: the first clinical trial of epigenetic restoration as a way to intervene in human aging and disease.

From theory to expectations

One reason the ITOA has traction in the field is that it offers a unifying way to think about a set of otherwise disconnected observations, without claiming to be the final word on aging.

For example, human aging follows a broadly similar script – graying hair, arterial stiffening, wrinkled skin, slower wound healing – despite wide genetic variation between individuals. In a purely damage-based view, this is puzzling: if damage accumulates randomly, why do so many people converge



INDUCIBLE CHANGES TO THE EPIGENOME (ICE) MOUSE (RIGHT), AND MOUSE OF THE SAME AGE (LEFT)
IMAGE SOURCE: IMAGE ADAPTED FROM YANG ET AL., CELL 2023

on the same symptoms late in life? With an ITOA framework, it's because what we share is not identical DNA sequences, but highly conserved epigenetic and repair systems. The same broad families of chromatin regulators, DNA-methylation enzymes, and damage-response pathways operate in all of us. If those shared systems lose information in stereotyped ways, they will tend to fail along similar trajectories, giving rise to familiar downstream problems: chronic inflammation, cellular senescence, mitochondrial dysfunction, stem cell exhaustion, and other "aging hallmarks" that show up across individuals and even across species.

The ITOA also connects naturally to the rise of epigenetic clocks, which are able to track chronological age reasonably well and can forecast risk of disease, disability and death across studies. If aging is the progressive loss of structured epigenetic information, then epigenetic patterns, such as DNA methylation, should provide a sensitive measure of how far an individual or organ has drifted from its youthful state. Newer "next-generation" clocks push this further by adding clinical data and other molecular readouts on top of methylation, and they seem to do a better job predicting healthspan and disease risk.[12] That is what an information-based view would predict: the more aspects of the system you measure, the more precisely you can place someone along their aging trajectory.

Perhaps most importantly, the ITOA provides a natural language for thinking about rejuvenation itself. Nuclear transfer experiments, when scientists place the nucleus of an old cell into an egg, can support development of a healthy young animal, showing that a "chronologically old" genome can, in the right context, give rise to young tissues. Epigenetic restoration with OSK, at least in current rodent and primate studies, can restore function in aged or injured tissues without obliterating cell identity. Together, these findings imply that the genome is not irreversibly aged in the way a rusted car frame is. Rather, the instructions for using that genome have been modified, and some aspects of those modifications are reversible.

Even so, the ITOA is not a finished "general theory." The aging field still lacks a framework that can, on its own, explain the wide variety of aging patterns seen across species, the effects of diverse longevity mutations, and why some interventions compress morbidity while others simply stretch late-life decline. Can epigenetic restoration address all of the famous Hallmarks of Aging, or only a subset? How many times is reset possible? The ITOA is one attempt to knit those observations together, but it will stand or fall on how well its predictions hold up in experiments and, eventually, in people.

Therapies for an information-based view of aging

The ITOA is woven into the logic behind ER-100's design: if aging reflects corrupted epigenetic instructions, then carefully nudging those instructions back toward youth might help damaged tissue recover. The Phase I trials in glaucoma and NAION are small, and focused mainly on safety but, whether these first trials reverse blindness or not, they mark a turning point in medicine. Rather than simply slowing further damage, the goal is to see whether epigenetic restoration can restore function in tissue that is already old or injured. Regardless of outcome, these studies will tell us something important about how far the epigenetic landscape in human tissue can be pushed and the risk that entails.

If ER-100 shows even modest benefit, the obvious next question is where else this technology might apply. Therapeutic epigenetic restoration could in principle be adapted to the liver, muscle, or nervous system, to target diseases that are currently considered irreversible. In an ITOA framework,

the goal is not just to patch one pathway at a time, but to restore cell identity and function by resetting the information that defines them. The hope is that, once that information is reset, cells can prevent and resolve disease on their own.

How we deliver that reset will inevitably diversify. Viral vectors are the first wave, but several groups are exploring alternative delivery routes, including lipid nanoparticles and small-molecule cocktails. At the same time, a growing number of companies – Life Biosciences, Retro Biosciences, Altos Labs, Rejuvenate Bio, NewLimit, and others – are racing to turn these concepts into medicines, backed by several billion dollars in investment and a vast R&D ecosystem. The approaches differ, but they share a common bet: if aging is fundamentally an information problem, then therapies that restore the right information could, in principle, treat many age-related diseases at once, rather than tackling them one pathway and one organ at a time.

Standing at the threshold

We return to the exam room, where the patient is still speaking with his doctor. The chart on the wall next to him remains blurred at the edges. Whatever happens next, something remarkable has already occurred: a person with glaucoma is being offered a clinical therapy which attempts to target cellular age.

Reaching this moment has taken far more than one person, one lab, or one theory. It grew from the slow realization that aging might be, at its core, a problem of lost biological information. Transforming that idea into testable models, experimental tools and ultimately into a clinical-grade therapy has required decades of work, thousands of experiments, and the sustained effort of many scientists, funders, and institutions.

Whether ER-100 ultimately benefits this patient is what the early trials aim to determine. What is already evident is that the field has crossed a threshold. We are no longer only documenting the erosion of cellular information. We are beginning to explore whether it can be restored. For the patient in the exam room, and for everyone who will grow old, that shift marks the start of a new phase in aging research, where the information in our cells is not only something to map, but something we may one day recover.

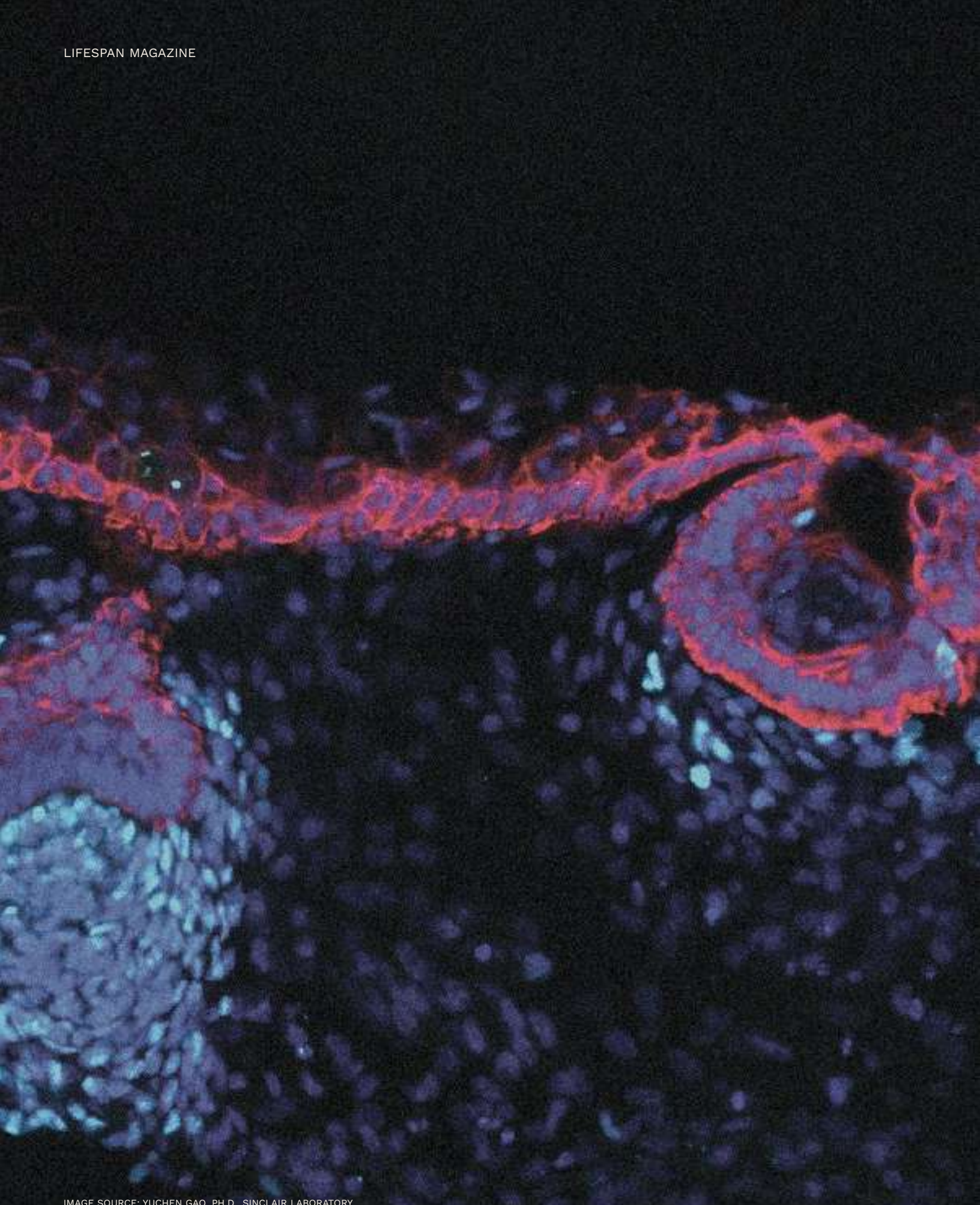


IMAGE SOURCE: YUCHEN GAO, PH.D., SINCLAIR LABORATORY

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THE ARCHITECTURE OF WOMEN'S AGING

BY KELLY RICH, MS, CGC, PHD

IMAGE SOURCE: VUSAL IBADZADE VIA UNSPLASH

“Aging for women is far more than wrinkles, step counts or the infamous “biological clock”. It is tightly linked to the life history of the ovaries, from their maturation in puberty to their silence after menopause.”

IMAGE DESIGN BY KELLY RICH, MS, CGC, PHD VIA CANVA AI

If you are a woman in 2026, you live in a low hum of health advice. Have children, the birthrate is falling. But also, it is fine not to have them, because your worth isn't measured in babies. But as a backup plan, consider freezing your eggs. Track your cycle. "Balance" your hormones. Take hormone therapy. Avoid hormone therapy. Walk more. Lift weights. Sleep better. Get off your phone. On and on and on. If you opened your inbox or Instagram between meetings today, you probably saw a version of at least three of those.

Some of this is helpful, some of it is opportunistic marketing, forever inventing new things for women to fix and buy. A fair amount is built on research that, for much of the last century, included few women and rarely asked how female biology might differ from male biology. Aging science has often treated a male body as the default. Only in the last decade have researchers begun to map how men and women age differently in a systematic way.[1–3] As that work has unfolded, one organ keeps coming up as unusually important for women's aging: the ovary.

Any reader worth her salt is rolling her eyes right now. *Obviously* the ovary is important to women's aging, it is one of the few organs that clearly differ between male and female bodies. But science has mostly treated ovaries as baby-making equipment, relevant when a woman wants a pregnancy and an afterthought once her periods stop. From puberty onward, though, the ovaries are doing far more than releasing eggs. They send pulses of estrogen and progesterone to the brain, heart, bones, and immune system. And somewhere around 50, they fall quiet.

Menopause is usually framed as the end of fertility, but that shutdown also marks a turn in risk for dementia, heart disease, osteoporosis, and other conditions – a turn that is even sharper for women who go through menopause unusually early.

Seen this way, aging for women is far more than wrinkles, step counts or the infamous "biological clock". It is tightly linked to the life history of the ovaries, from their maturation in puberty to their silence after menopause. If you care about whether women reach old age with their memory, mobility, and independence intact, ovarian aging belongs at the center of the conversation. And if ovarian timing matters that much, the real question is whether changing when and how menopause occurs could change the entire trajectory of women's aging.

Living longer, feeling older

Public health data have been consistent for decades: women outlive men almost everywhere in the world. In some countries the gap in average lifespan approaches ten years.[4] The catch is that many of those extra years are spent with more frailty, disability, osteoporosis, dementia, and other chronic conditions. Researchers call this the male–female health survival paradox.[5,6]

A few broad biological quirks seem to feed into it. Genetically, women carry two copies of the X chromosome, with built in redundancy for thousands of genes. Men's single X is more exposed to harmful mutations acquired over a lifetime, an idea sometimes called the "unguarded X" hypothesis.[7] Women's immune systems tend to be stronger and age more slowly, which helps them survive infections but also raises the risk of autoimmune disease.[8] And when scientists use DNA methylation and other markers to build "biological aging clocks," men usually come out older than women of the same chronological age. But the hormonal changes of menopause are themselves associated with an acceleration in women's biological aging.[9,10]

All of this loops back to what the ovaries are doing. For roughly four decades, they secrete estrogen and progesterone in carefully timed pulses. Those hormones do far more than prepare the uterus for pregnancy. They talk to the brain, the cardiovascular system, bone, fat, and immune cells. When ovarian function declines and then stops, that hormonal conversation changes abruptly.

You can think of it this way: men tend to age along a relatively smooth curve, while women age in chapters. The same ovarian system that supports pregnancy and early life survival seems to set women up for a different pattern of vulnerability later, once that system winds down. This is the starting point for rethinking menopause as far more than the end of fertility.

How an ovary gets old

Most of the story we tell about ovarian aging revolves around one number: egg count. You are born with one to two million oocytes and by puberty only a few hundred thousand remain. Every month, more are lost. When the egg reserve falls below a certain threshold, cycles become erratic and then stop.

That picture is not wrong, but it is incomplete. It treats the ovary like a warehouse with dwindling stock. In reality, it is a small but powerful organ with distinct neighborhoods – different kinds of tissues that age, and in some ways fall apart, long before the last egg is gone.

Roughly speaking, the ovary has two main components. The outer layer, the cortex, is where follicles live. Each follicle is a tiny pocket that holds an immature egg surrounded by helper cells and, as it grows, can fill with fluid. Deeper inside is the medulla, packed with blood vessels and connective tissue. Over time, follicles grow and either release an egg or quietly break down. The ovary, as a whole, is held together by a mesh of structural proteins and stromal cells, threaded with nerves and capillaries. Whether a follicle develops properly depends not just on the chromosomes inside the egg, but also on how stiff the surrounding tissue is, how much blood reaches it, and what mix of hormones and growth factors nearby cells are sending its way. In this context, an egg is only as healthy as the tissue around it.

With age, that environment shifts. In mouse and human ovaries, the tissue around follicles shows thicker, denser, more scar-like material, all classic signs of fibrosis.[11] Collagen builds up, the cortex hardens. Follicles then sit in a physical environment that makes it harder for them to expand and for an egg to be released at ovulation. Fibrosis can also warp hormone gradients and pinch the tiny vessels that feed follicles. Studies comparing young and old ovaries find that sympathetic nerves around follicles become more abundant with age, and that stromal cells such as fibroblasts shift toward inflammation and scarring – changes that may mark declines in follicle health and overall ovarian function.[12]

Taken together, these tissue-level changes look less like harmless background and more like active drivers of ovarian aging. The striking part is that some of them appear at least partly reversible. In one experiment, researchers delivered the anti-fibrotic drug pirfenidone, already approved for pulmonary fibrosis, to “reproductively old” mice. Within weeks, ovarian collagen decreased and more than half of previously anovulatory animals ovulated again; their eggs could be fertilized and grown to blastocysts *in vitro*.[11] Shorter treatment in slightly younger mice also reduced fibrosis and increased the number of eggs released, without changing the ovaries in young controls.

At the moment, no one is prescribing pirfenidone as a fertility drug for humans as its effects on ovar-

ian aging have only been shown in mice. But findings like this support a central idea: the ovary is an organ whose aging may one day be modulated, not just endured. If that is true, the next question is what happens to the rest of the body when the ovarian clock speeds up – or when it slows down.

What happens when the ovaries go quiet

Clinically, menopause is defined as twelve months without a period. Biologically, it's a major transition for several organ systems simultaneously. There's also a long list of familiar symptoms – hot flashes, sleep disruption, mood changes, vaginal dryness, shifts in body composition – that can make everyday life feel very different. The menopause-related changes in the brain and cardiovascular system, however, are most strongly tied to long-term outcomes: dementia risk, heart disease, and ultimately how long and how well people live.

The brain is dense with estrogen receptors, especially in regions that regulate memory, mood, sleep, and body temperature. From puberty onward, these brain regions have been running in the background on a relatively steady stream of ovarian estrogen. When that signal drops, both brain metabolism and structure shift. Longitudinal imaging studies find that women moving through menopause show reduced glucose metabolism and gray matter volume in specific regions, along with more amyloid deposition, compared with age-matched men and premenopausal women.[13–16] Some of these patterns resemble early changes seen in Alzheimer's disease.

Most women experiencing menopause report hot flashes and night sweats. Frequent vasomotor symptoms like these have been linked to small vascular lesions in the brain and to blood-based biomarkers associated with future dementia risk.[17] For many women, cognition stabilizes after the transition. Still, women overall are more likely than men to develop dementia in later life.

The cardiovascular system also pivots. Before menopause, women on average develop heart disease about ten years later than men, a gap often attributed to estrogen's protective effects on blood vessels. After menopause, blood pressure and LDL cholesterol tend to rise, arteries stiffen, and women's risk of heart disease begins to catch up.[18]

Timing matters here. The earlier the ovaries fall silent, the steeper the consequences. Women who go through surgical menopause, having both ovaries removed, show faster cognitive decline, more Alzheimer's type pathology, and higher dementia risk than women with intact ovaries.[19] Premature ovarian insufficiency and very early natural menopause, before about 40, are linked to higher overall and cardiovascular mortality and more osteoporosis.[20]

Natural menopause at the typical age, around 51, still marks an uptick in risk, but how big that jump is depends heavily on midlife blood pressure, weight, smoking, and glucose control. Put together, these patterns have led some researchers to a blunt question: if ovarian shutdown is such a powerful pivot, do women whose ovaries keep working longer actually live longer?

IMAGE SOURCE: ESIN DENIZ VIA ADOBE STOCK

When the ovaries take their time

Across multiple cohorts, the answer appears to be yes – modestly but consistently. In the Women's Health Initiative, a study of more than 16,000 women, those with a reproductive lifespan longer than 40 years (from first period to menopause) had about 13 percent higher odds of reaching age 90 than those with less than 33 reproductive years, even after accounting for smoking, BMI, and other factors.[21] A Swedish twin cohort found that women with 40 or more reproductive years had lower all-cause mortality and about 0.8 extra years of life than those with 34 or fewer.[22]

Cardiovascular outcomes point the same way. In a Chinese cohort, each additional year of reproductive lifespan was associated with about a 2 percent lower risk of cardiac death.[23] Other work links later natural menopause and longer reproductive span with longer telomeres in white blood cells and "younger" brain-age metrics on MRI.[24,25]

The flip side is just as telling. Analyses of the National Health and Nutrition Examination Survey (NHANES), a long-running U.S. health survey, show that women with premature menopause and very short reproductive lifespans have higher mortality and shorter life expectancy.[26] Removing both ovaries before natural menopause (surgical menopause) amplifies that risk further, especially for dementia and cardiovascular disease, unless women receive hormone therapy tailored to their age and health history.

These are correlations, not guarantees, and the effect sizes for any one woman are small. No one earns a decade of extra life from a slightly later last period. Taken together, though, the signal is hard to ignore: women whose ovaries function for longer tend to have longer and healthier lives.

Under the hood, genetics does a lot of the steering. Twin and family studies estimate that 40 to 50 percent of the variation in age at natural menopause is heritable; mothers, daughters, and sisters show parallel patterns.[27,28] Even brothers of women with later menopause have a survival advantage.[29] Large genome-wide association studies link later menopause to variants in DNA repair pathways, FSH signaling, and IGF1 and mTOR pathways – the same circuits implicated in cancer, cardiovascular disease, and lifespan more broadly.[30,31] In animal experiments, transplanting young ovaries into older mice extends the older animals' lifespan, even when the grafted ovaries cannot produce eggs, which suggests that ovarian hormones themselves, not just fertility, are protective.[32,33]

Seen in that light, the infamous "biological clock" looks less like a timer counting down to the last viable egg and more like a gauge of how long the ovaries keep sending protective signals to the rest of the body. That reframing leads directly to the question driving a new wave of research: if later menopause and longer ovarian function are linked to better outcomes, can we safely nudge that timing?

"The infamous "biological clock" looks less like a timer counting down to the last viable egg, and more like a gauge of how long the ovaries keep sending protective signals to the rest of the body."

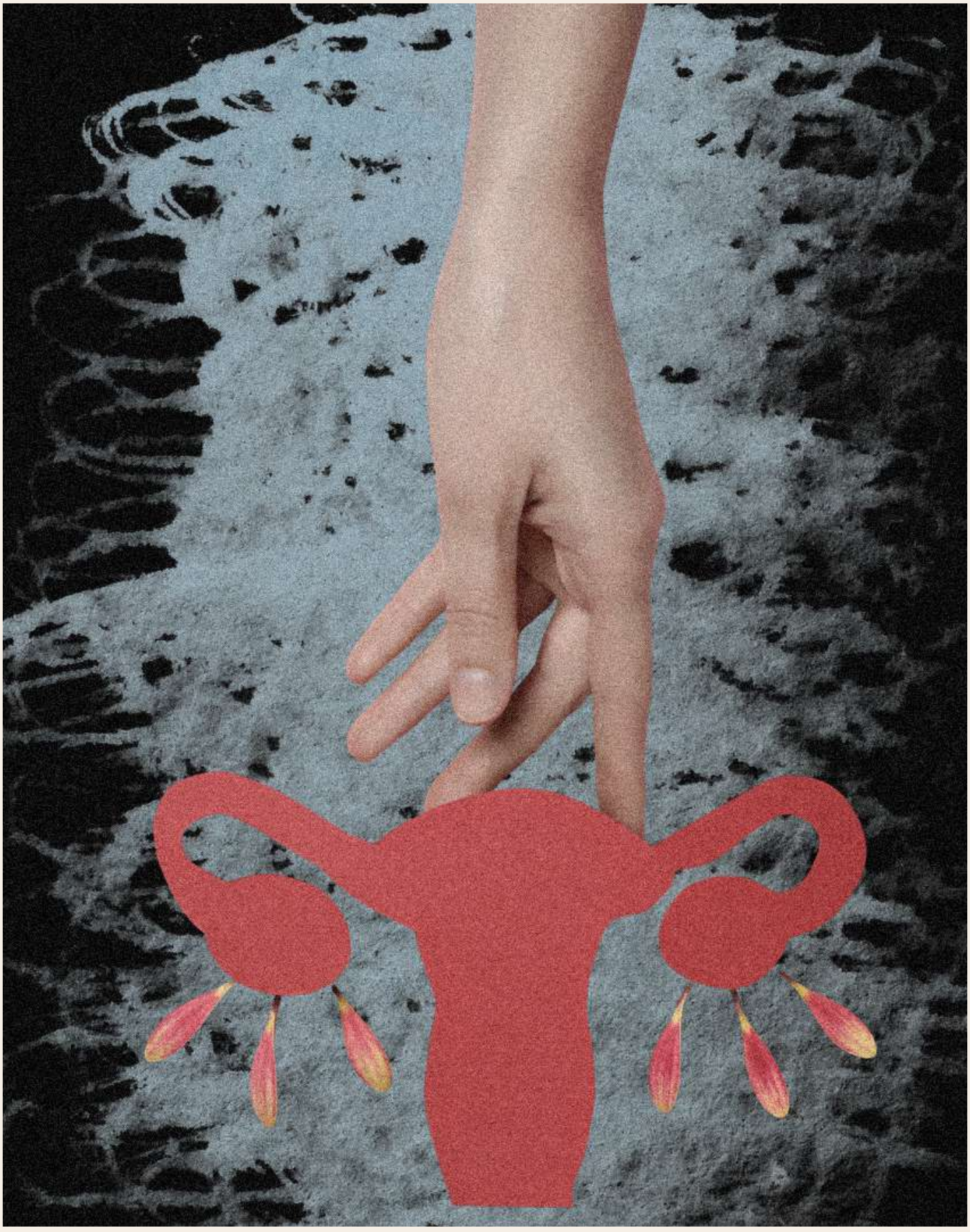

IMAGE DESIGN BY KELLY RICH, MS, CGC, PHD VIA CANVA

Can we safely delay menopause?

No one is promising pills that will keep 70-year-olds ovulating. But several experimental approaches are circling the same target: slowing ovarian aging by preserving follicles and easing the tissue-level changes that eventually tip the ovary into menopause.

One line of work targets fibrosis. The pirfenidone experiments in mice suggest that reducing ovarian scarring can restore ovulation in reproductively old animals.[11] Researchers are now testing other anti-fibrotic strategies in animal models to see whether easing stiffness and collagen buildup can not only prompt ovulation but also shift hormone profiles and delay the final shutdown.

Another strategy uses anti-Müllerian hormone (AMH), produced by growing follicles, which normally acts as a brake on the activation of the primordial follicle pool. High AMH levels keep more follicles in reserve; low levels allows more follicles to move into active growth, where most are eventually lost.[34] Pharmaceutical AMH analogs are currently being tested in animals to see whether pressing harder on that AMH brake can reduce the number of eggs lost each cycle and extend the ovarian reserve.

Then there are the drugs that have become darlings of the aging research world. In middle-aged mice, chronic low-dose metformin – a diabetes medication that has attracted interest as a possible geroprotective – increased the number of primordial and primary follicles, improved estrous cycles and estradiol levels, reduced oxidative damage, and upregulated the longevity-linked protein SIRT1 in the ovary, consistent with delayed ovarian aging and a healthier microenvironment.[35] mTOR inhibitors are on the list too. mTOR is one of the body's main nutrient-sensing switches; dialing it down in animals extends lifespan and appears to preserve ovarian reserve for longer. A clinical trial at Columbia University is now testing rapamycin, an mTOR-inhibiting immunosuppressant that extends lifespan in mice, in women aged 35 to 45 to see whether it changes measures of ovarian reserve. Alongside these pathway-targeting drugs, some fertility clinics offer a range of so-called "ovarian rejuvenation" procedures. These include injecting platelet-rich plasma directly into the ovaries, delivering stem-cell-based products, and even transferring mitochondria into oocytes.[36] Some small studies report changes in surrogate markers such as AMH levels, follicle count, or oocyte yield after these procedures, but so far they have not consistently translated into higher rates of healthy embryos, ongoing pregnancy, or live birth.

All of this work is early and still mostly proof of concept, and we must be careful about how we read it. Most studies are in rodents and human trials are just beginning. At a deeper level, the field is starting to sort out what it would mean to truly slow ovarian aging, rather than simply squeeze a few more eggs out of an already stressed organ. Much of the most interesting work now zeroes in on the ovarian microenvironment – fibrosis, blood flow, inflammatory signaling, and nutrient-sensing pathways like mTOR – asking whether easing scarring or dialing down overactive growth signals can preserve existing follicles and maintain hormone production for longer. That is a very different goal from transiently "activating" dormant follicles to boost egg retrieval in the short term, which may actually accelerate the depletion of the ovarian reserve.

No one knows what the long-term trade-offs will be, and there are real biological reasons to be cautious. Later natural menopause is associated with a slightly higher risk of breast and endometrial cancer, likely due to more years of estrogen exposure,

A framework for aging, with ovaries in mind.

By now it should be clear there is no master supplement stack or perfect hormone regimen. What the data do offer is a way to read your own history and the flood of advice through an ovarian lens. Here are five filters to help organize it.

Treat reproductive timing as a health signal, not just a fertility alarm.

Age at first period, cycle regularity, age at menopause, and total reproductive lifespan carry information about later risk for cardiovascular disease, osteoporosis, and dementia, especially when menopause arrives unusually early. They belong in the same mental bucket as family history or blood pressure – cues for monitoring and topics to raise with your clinician.

Protect the midlife pivot.

For most women, the late 40s and early 50s are when ovarian function winds down and curves for heart disease, bone loss, and cognitive changes start to steepen. That is why timing matters so much for things like hormone therapy, blood-pressure and lipid control, GLP-1 drugs, and mood treatment: the same intervention has different implications depending on its timing.

Be skeptical of one-size-fits-all longevity hacks.

Intermittent fasting protocols, supplement stacks, and mTOR- or NAD^+-targeting regimens were often built and tested in male animals. For women, especially those who are premenopausal or recently menopausal, that means approaching these interventions as hypotheses to test in your own body, not universal rules.

See weight and metabolism in terms of future muscle, bone, and brain.

Weight-loss and glucose-lowering drugs can dramatically improve cardiometabolic markers, especially for women entering menopause with obesity or diabetes. At the same time, midlife is when women have accelerated loss of lean mass and bone density, so approaches that decrease fat at the expense of muscle and skeleton needs to be understood in terms of trade-offs.

Think in stages, not lifelong rules.

The levers that matter most shift over time: building peak bone and muscle in youth, recognizing cycle patterns and inflammatory conditions in the reproductive years, focusing on vascular health, sleep, mood, and time-sensitive hormone decisions around menopause, then emphasizing strength, balance, cognition, and social connection later on. The ovaries eventually retire, but the architecture they helped build is what you are living in, and different parts of that structure will need attention at different times.

even as it links to lower cardiac death and slightly longer life overall.[37] Extending ovarian function pharmacologically could sharpen that tension. Beyond this, keeping the ovaries online longer might also mean more years of managing contraception, with unclear implications for pregnancy risk at older ages.

Most women alive today will never take pirfenidone for ovarian fibrosis or enroll in a rapamycin trial. But the emerging science still matters. It shifts menopause from a mysterious cliff to a biological process with moving parts – some of which might, one day, be adjustable. And it sharpens the picture of what "aging well" means for women right now, and how paying attention to ovarian cues can pay off.

Centering ovaries in the future of women's health

For most of medical history, the ovaries were treated as switches for fertility: on, then off. The rest of women's aging was filed under "general medicine" or (let's be honest) "mystery". The emerging picture is less dimmer-switch, more master control room. The ovaries are wired into the brain, heart, immune system, and skeleton, sending signals that shape how the whole system weathers time.

We are only just starting to see what it might mean to adjust that wiring on purpose. Anti-fibrotic drugs, AMH analogs, and rapamycin trials are early, cautious attempts to investigate whether we can delay or soften ovarian shutdown without trading hot flashes for a different kind of disaster. So far, the cutting edge looks exciting, but it is also small, experimental, and a long way from anything women should be trying on their own outside carefully run clinical trials.

Meanwhile, the boring stuff remains fundamentally powerful. Controlling blood pressure, building and keeping muscle, not smoking, sleeping like it matters, taking statins or GLP-1s when they're indicated – these are still the most reliable levers for extending healthy life, including for women whose ovaries are coasting toward, or already well past, menopause.

If ovaries are the major architects of health in female bodies, the task now is to fund, run, and take seriously the science that treats those architects as more than baby makers. That means clinical trials which include women in real numbers, basic research that does not assume the male body is the default setting, and policy that treats menopause as a systemic transition rather than a punch line. Developing real therapeutic options will require adequately-powered randomized trials with standardized protocols and hard endpoints (not just AMH or follicle counts), long-term safety data on cancer and metabolic risk, and regulatory frameworks that clearly distinguish experimental procedures from established care.

We are still early in this story, but the shift is already profoundly hopeful. A generation ago, menopause was something women were expected to endure in silence. Today, we can point to pathways, trials, and concrete levers that link ovarian timing to how long our brains, hearts, and bones stay resilient. Paying attention to ovaries is not about worshipping fertility. It is about finally centering an organ that has been quietly steering women's health all along, and using that insight to design better research, better treatments, and better odds of staying sharp, strong, and independent into old age. The more precisely we understand what ovaries are doing, the more leverage we have to turn added years of life into years of health.

"Paying attention to ovaries is not about worshipping fertility. It is about finally centering an organ that has been quietly steering women's health all along, and using that insight to design better research, better treatments, and better odds of staying sharp, strong, and independent into old age."

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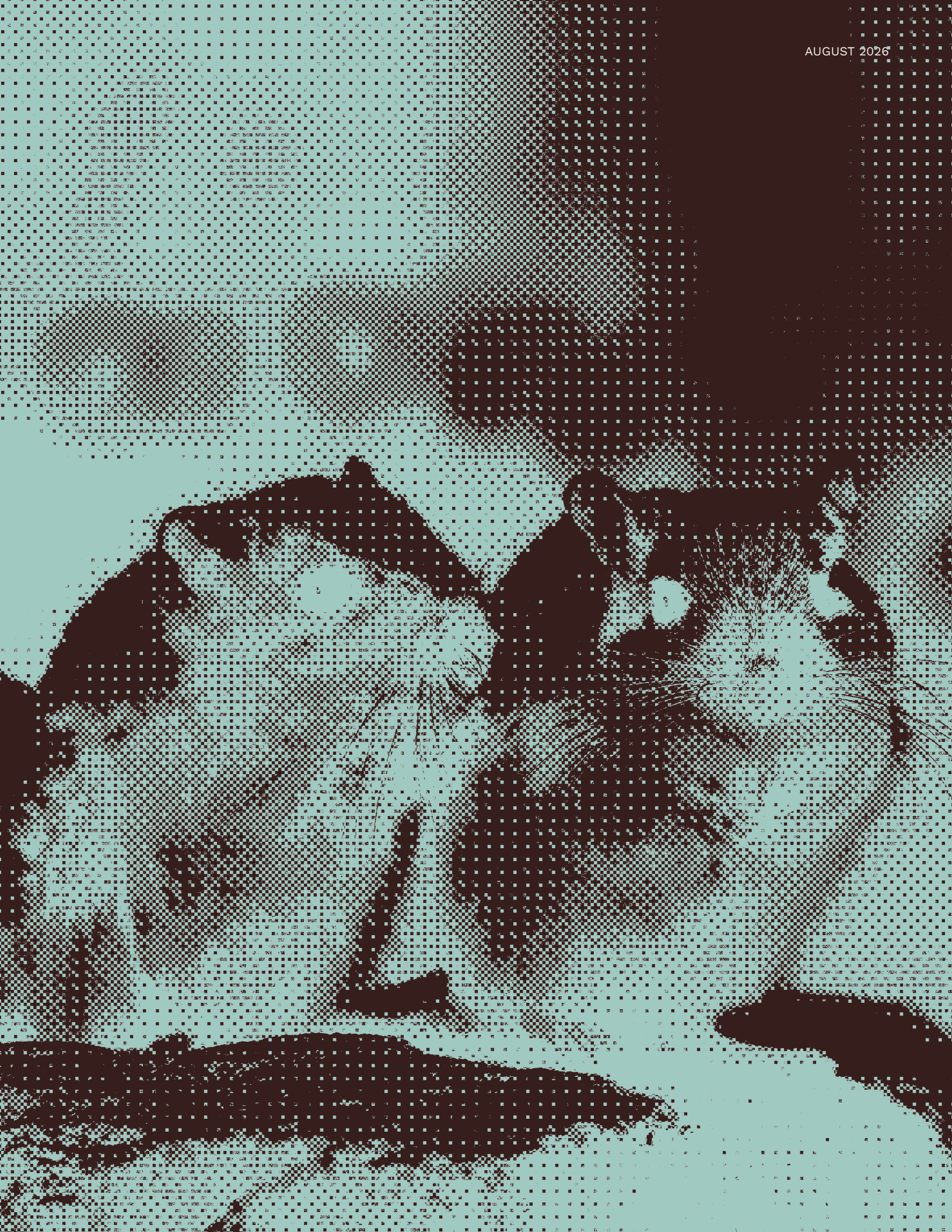
THE "LOVE HORMONE" THAT ADDS 73% MORE LIFE (TO MICE)

BY ADIV JOHNSON, PHD

IMAGE SOURCE: SIMONE-DINOIA VIA UNSPLASH

AUGUST 2026



The importance of longevity science

Several years ago, I got stuck in a monstrous traffic jam while heading to the Phoenix airport on Interstate 10. It was the kind of situation where cars were completely stuck and barely inching forward. The traffic jam itself lasted more than two hours and, afterwards, huge numbers of people pulled into the next rest stop on the highway.

I pulled into this rest area and remember seeing an elderly couple holding on to each other and walking very, very slowly to the restrooms. It was clear that this everyday task of simply walking to the bathroom was not a trivial feat for these two. The woman was wearing large sunglasses and I could hear her reminding her husband that she couldn't see very well and was relying on him to guide her.

For some reason, this scene stuck with me. Not only did I feel an intense sense of empathy for this couple, but it was also a poignant reminder of why longevity science and medicine are so important.

Ultimately, we all want to maintain high levels of functionality and independence and compress the gap between frailty and death as much as possible.

A new study testing a unique drug combination

With this in mind, a recent study published in the scientific journal *Aging* shows what might one day be possible.[1] This work, which comes out of the laboratory of Dr. Irina Conboy at the University of California, Berkeley (the same lab that showed replacing plasma extends mouse lifespan) found that a combination of the love hormone oxytocin (Oxt) and A5i, an inhibitor of a protein called Alk5 (also known as TGF-β receptor type-1), extends the remaining lifespan of older, frail mice by a shockingly large amount. The remaining lifespan in older male mice was extended by 73.73% and what makes this study unique is that the mice didn't receive this cocktail of drugs until they were already very old.

Why combine these two molecules? Because aging shifts the body's chemistry in opposite directions. Oxytocin is a hormone made of just nine amino acids and produced mainly in the brain. For decades, scientists have known it for its role in childbirth and breastfeeding, where it helps trigger labor and allows mothers to release milk. But over time, researchers discovered that oxytocin does much more than that. It also plays a role in trust, social bonding, and emotional connection, which is why it is often nicknamed the "love hormone".[2]

The story of oxytocin's discovery is also a fascinating chapter in the history of biology. In the early 1900s, scientists noticed that extracts from the pituitary gland could cause the uterus to contract. For years they didn't know exactly what the active substance was. It was not until the 1950s that American biochemist Dr. Vincent du Vigneaud finally determined oxytocin's chemical structure and figured out how to make it in the laboratory. This achievement was a major milestone because it marked the first time a hormone had been fully synthesized, earning du Vigneaud the Nobel Prize in Chemistry in 1955.

Today we know oxytocin has effects far beyond childbirth. It helps strengthen human relationships, influences social behavior, and even plays a role in repairing damaged tissues such as muscle. Levels of oxytocin reportedly decline as we get older, which has led scientists to wonder whether restoring it later in life might help maintain health and resilience.

“Ultimately, we all want to maintain high levels of functionality and independence and compress the gap between frailty and death as much as possible.”

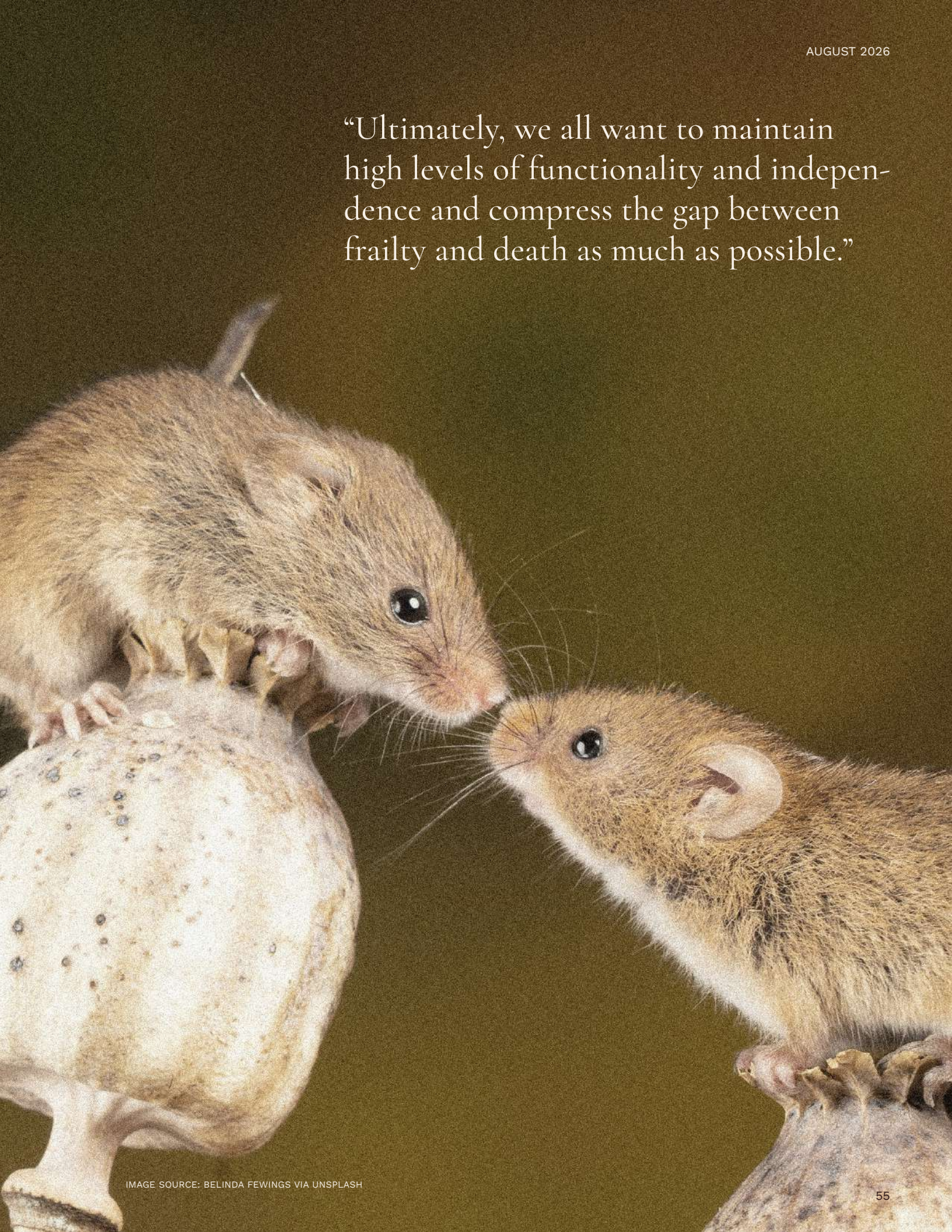


IMAGE SOURCE: BELINDA FEWINGS VIA UNSPLASH

In animal studies, a lack of oxytocin matters. Mice that cannot produce oxytocin develop muscle wasting earlier in life, and restoring oxytocin helps regenerate aging muscle.[3] There is also evidence that oxytocin can dampen several biological hallmarks of aging in model organisms.[4] In humans, it already has FDA approval for use in obstetrics, which means its biology is at least somewhat understood.

At the same time, as we get older, evidence suggests that another pathway is moving in the opposite direction. TGF-β signaling, a key regulator of inflammation and tissue remodeling, increases with age. When overactive, it can drive chronic inflammation and impair the body's ability to repair itself. [5] The idea behind the therapy is simple: restore balance. Boost what declines with age and suppress what rises too much. Oxytocin replaces a signal the body is losing, while A5i blocks excessive TGF-β activity.

In 2019, researchers tested this combination in older mice.[6] The results were striking. Together, oxytocin and A5i reduced neuroinflammation, improved cognitive function, rejuvenated liver and muscle tissue, and lowered markers associated with zombie-like senescent cells. The findings suggested that correcting this age-related signaling imbalance might restore multiple aspects of tissue function at once.

"Levels of oxytocin naturally decline as we get older, which has led scientists to wonder whether restoring it later in life might help maintain health and resilience."

Remarkable longevity results

In the more recent study,[1] mice that were old and frail were treated with oxytocin and A5i starting at 25 months of age, which is roughly equivalent to 75-year-old humans. Mice were injected with either a control injection or oxytocin and A5i on Mondays, Wednesdays, and Fridays. The protocol itself followed a cyclical pattern where the drugs were administered under the skin for two weeks and then stopped for two weeks before the next round of treatment.

What stood out in this paper wasn't just that lifespan was extended, but by how much. The combination of oxytocin and A5i increased additional life expectancy by 73.73% in male mice. What this means is that, starting from the time these mice received these drugs, they lived 73.73% longer than mice that weren't given oxytocin and A5i. If you zoom out and look at their entire lifespan – from birth until death – this translates to a 14% average difference between mice given the drugs and control mice. Dr. Conboy, the corresponding author for this study, emphasized that "this effect was observed in already frail, old mice analogous to 75- to 80-year-old people."

To give you a sense of how substantial this report is, I previously published a short paper that summarized all of the successful lifespan studies conducted by the Interventions Testing Program from the National Institute on Aging.[7] One comparable study involves rapamycin – the gold standard compound for extending lifespan in mice by inhibiting the longevity pathway mTOR – which was given to mice starting at 20 months of age. Rapamycin extended average lifespan by 11% in males and 15% in females.[8] This new study is up there with rapamycin for males, the current world champion molecule for extending mouse lifespan.

Visually, the mice treated with oxytocin and A5i looked healthier and less frail. The male mice also performed better on a treadmill and had superior cognition, which means their brain function was improved. While female mice did not experience these healthspan benefits, a separate assessment did find that oxytocin and A5i treatment increased the number of pups in middle-aged female mice.

Another interesting result involved changes in the proteome, which is the full set of proteins circulating in the body. Proteins carry out most of the work inside our cells, like getting rid of junk and moving nutrients and other components to where they need to go. They're basically molecular robots that get things done, and their levels change in predictable ways as we age. Because of this, scientists are able to estimate a person's age by measuring patterns of proteins in the blood.

In this study, the researchers examined how oxytocin and A5i affected blood proteins in older mice. After just seven days of treatment, the overall pattern of proteins began to resemble the profile normally seen in younger animals.

The team also looked at something called biological noise. As organisms age, many proteins become more chaotic in their expression, meaning their levels fluctuate more from moment to moment. One example is Interleukin-6 (IL6), a classical inflammatory protein. A really high-quality, robust study previously published by Dr. Tony Wyss-Coray showed that IL6 tends to increase with age in human blood.[9]

Treatment with oxytocin and A5i reduced this age-related variability in both male and female mice. Further computer-based analysis suggested that several biological signaling pathways were shifted back toward more youthful patterns, including pathways related to inflammation such as TNF signaling.

If these findings are reproducible, they are impressive. Of course, it is far too early to know if any of these effects would translate to humans. If such effects could translate, however, it would not just mean living longer. It would mean spending those extra years with better strength, sharper cognition, and greater day-to-day functioning – extending the period of life when people can truly enjoy their independence.

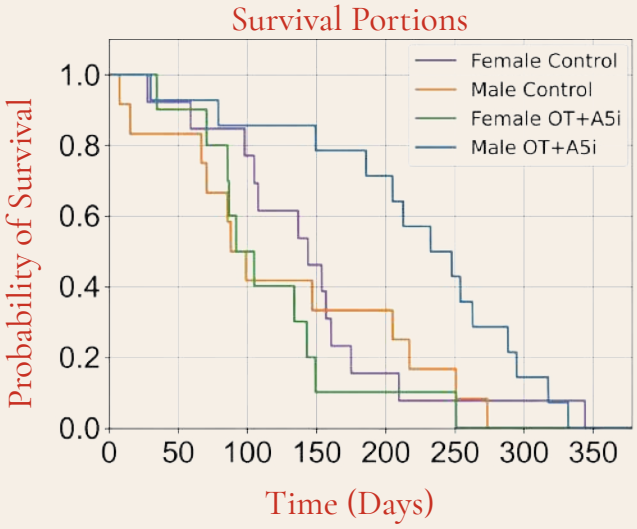


IMAGE SOURCE: KATO ET AL., AGING (ALBANY) 2025, UPSCALED BY AI

Putting the results into context

The results are exciting, but it is important to keep a few caveats in mind before drawing big conclusions.

First, the study used a specific laboratory mouse strain called C57BL/6, often referred to as "Black 6" or "B6". These mice are highly inbred, meaning they are genetically almost identical to one another. That uniformity makes experiments easier to control, but it also creates a potential problem when trying to translate findings to humans. People are genetically diverse, and a treatment that works well in a single inbred strain could be benefiting from quirks unique to that genetic background.

This strain also differs from humans in another notable way. In Black 6 mice, males typically live longer than females – the opposite of what we see in people, where women generally outlive men.

Another limitation is the relatively small number of animals used in the study. Each of the four groups (the oxytocin and A5i or control groups for both males and females) contained between 10 and 14 animals. With numbers that small, there is always the possibility that chance events can skew the outcome. For example, if enough mice in the male control group happened to die earlier than expected, it could exaggerate the apparent benefit of the treatment.

Finally, the lifespan extension was observed only in males, not females. While that may seem concerning at first glance, sex-specific effects are actually quite common in aging research.[10] Many interventions that influence lifespan in mice show different outcomes depending on whether the animals are male or female.

In other words, the findings are genuinely intriguing – but as with any early study, they will need to be repeated and tested in additional models before we know how broadly they apply. Concerns about reproducibility were one of the main reasons the National Institute on Aging created the Interventions Testing Program. Over time, it became clear that many lifespan studies in mice – often performed in a single lab using small numbers of genetically identical animals – could not always be reproduced. The Interventions Testing Program was designed to address that problem.

Instead of testing interventions in a single strain of mice at one institution, the Interventions Testing Program evaluates compounds using large numbers of genetically diverse mice housed at multiple research centers across the United States. The idea is straightforward: if a treatment truly affects aging, it should show benefits across different populations of animals and in different laboratories.

One example is the simple amino acid glycine. When tested through the Interventions Testing Program, glycine significantly extended lifespan in both male and female mice.[11] Importantly, the study included far larger cohorts than most traditional lifespan experiments: 280 female control mice, 136 glycine-treated females, 300 male controls, and 156 glycine-treated males. With numbers like these, researchers can be much more confident that a positive result reflects a real biological effect rather than chance.

At the same time, the program has its critics. Some proponents of the Interventions Testing Program have, at times, taken a rather dogmatic view – implying that if a compound fails to extend lifespan in the program, it should be dismissed entirely. That stance may be too rigid. A therapy that does not produce a lifespan signal in mice could still improve human health, resilience, or quality of life. There are actually examples of therapies that work in humans, but not mice, so it's important to re-

member that mouse data is not the be-all, end-all. In other words, the Interventions Testing Program is an important tool for testing robustness, but it should not be treated as the sole gatekeeper for promising interventions in aging biology.

Looking to the future

Even with these limitations, the findings are exciting enough to justify much deeper investigation. A logical next step would be to repeat the study in larger cohorts of genetically diverse mice to see whether the effect holds up under more rigorous conditions. Researchers will also need to refine the dosing of both compounds. The optimal balance between oxytocin and A5i may be very different from what was used in this initial experiment.

Another important question is how each molecule contributes to the effect. Does oxytocin drive most of the benefit while A5i simply removes an inflammatory brake? Or is the power of the intervention truly in the combination – restoring a youthful signal while simultaneously blocking an age-related one? Understanding that biology could reveal new therapeutic targets and help researchers design even more effective treatments.

There are also interesting mechanistic questions. How exactly does the treatment work? By improving tissue regeneration? By lowering the burden of senescent cells? Or could it be acting through the brain, altering systemic signals that coordinate aging across the body? Answering these questions could teach us far more about how aging itself is regulated and unlock more powerful therapies.

Oxytocin itself is not an obscure molecule. It has long been used medically in obstetrics and versions of oxytocin nasal sprays are even sold online. That accessibility makes the science even more important to interpret carefully. Self-experimentation based on early animal studies is rarely wise, and the safety, dosing, and long-term effects of medically unsupervised oxytocin use remain uncertain.

Ultimately, progress will depend on carefully designed human studies. Placebo-controlled safety trials will be essential to determine whether this combination is safe, well tolerated, and biologically active in people.

For now, the study should be viewed for what it is: an early but provocative signal. If the results prove reproducible, they hint at something powerful – that correcting age-related signaling imbalances might restore multiple aspects of tissue function at once. In the long arc of longevity science, discoveries like this are often the first glimpse of entirely new ways to intervene in aging. In email correspondence, Dr. Conboy put it perfectly: “Future work is clearly needed to unravel the biomedical mechanisms and test clinical implications.”

IMAGE SOURCE: AHMET YÜKSEK VIA UNSPLASH

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INTERVIEW

BEYOND YOUR BIRTHDAY:

STEVE HORVATH ON THE SCIENCE OF EPIGENETIC AGING

BY KELLY RICH, MS, CGC, PHD

IMAGE SOURCE: DIYA POKHAREL VIA UNSPLASH

ILLUSTRATED BY
DAVID A. SINCLAIR, AO, PHD

Dr. Steve Horvath is a biostatistician and researcher best known for discovering "epigenetic clocks," mathematical models that estimate a person's biological age by reading chemical tags known as DNA methylation.

While your birthday counts how many years you've been alive, Horvath's original clock, as well as the many biological age clocks inspired by it, reflect how fast your body is really aging. These clocks have opened a new window into the biology of getting older, revealing that people with different diseases, lifestyles, or treatments can look biologically older or younger than their calendar age. Here, Dr. Horvath reflects on how this idea emerged, what epigenetic clocks can (and can't) tell us about health, and how they might reshape the future of aging research.

1. Before you built your first epigenetic clock, did you actually expect there to be a "clock" hiding in DNA methylation, or did the data surprise you?

It was a complete surprise. I had been working hard on building age predictors based on gene expression data. When I turned to DNA methylation, I did not expect to find anything as striking as what emerged. The accuracy was extraordinary: the predictions matched people's ages with a Pearson correlation above 0.9, which in this context means an extremely tight relationship between predicted and actual age across a broad spectrum of ages.

I spent months calling these things "age predictors" or "biomarkers" before settling on the term "epigenetic clock." I felt the exceptional accuracy earned the label: these weren't rough estimates, they were clocks. I still distinguish the term "biomarker of aging" from that of clocks (defined as very accurate age predictors).

2. You were originally trained as a mathematician and biostatistician. How has that background shaped the way you think about biology and aging?

It was both a blessing and a curse. A blessing because it allowed me to see the signal through the noise. When I first looked at DNA methylation data in the context of aging, I immediately recognized that this was my future. I dropped my gene expression project without hesitation. And methylation never disappointed: it led to a series of increasingly powerful clocks, culminating in the pan-mammalian clocks that can measure age across all mammalian species. But my training was also a limitation. It took me many years to learn enough molecular biology and clinical medicine to put the clocks into proper biological and clinical context. Studying math and biostatistics is not the most direct path to becoming a geroscientist. Medicine or molecular biology may be more efficient routes for many students. Or focus on computational biology. Honestly, I would tell students: don't follow my exact tracks. And don't spend too much time in graduate school.

3. When researchers apply epigenetic clocks to almost any disease group (heart disease, diabetes, HIV, neurodegenerative diseases) they often see signs of accelerated epigenetic aging. Does this make you think that diseases are different faces of the same aging process? Or do you see disease and aging as separate processes that just happen to overlap in the clocks?

The situation is more complicated than either framing suggests. You have to be careful about which epigenetic clock is being used and which tissue is being analyzed. Clocks trained on bulk tissue capture both changes in cell composition (which cell types are present) and cell-intrinsic changes (what is happening inside each cell). These are very different biological signals. And clocks applied to blood may give a completely different picture from clocks applied to specific organs. For example, epigenetic age in the brain may bear little relation to epigenetic age in blood.

Overall, I view disease as fundamentally different from epigenetic aging. When an overlap is observed, the important question is: where exactly is the overlap? In which cell type? According to which clock? Without that precision, the apparent connection between disease and aging can be misleading. Only a subset of DNA methylation changes are actually causally involved in organ dysfunction.

4. You've helped develop clocks not just for humans but across many different species. What have those pan-mammalian clocks taught you about what is universal in aging, and what might be uniquely human?

I think the most stunning insight is that one can measure age across all mammalian species using several hundred CpG sites located in stretches

"I have watched the field go from skepticism about epigenetic clocks to serious drug development programs in barely a decade. We are not helpless in the face of aging anymore."

of DNA that are almost identical in every mammal (what scientists call "ultraconserved" regions). That finding shows that specific aspects of epigenetic aging are deeply conserved.

But I want to avoid oversimplification. Millions of positions on the DNA molecule show age-related changes that are specific to a particular tissue type and species. Methylation changes in enhancer regions, for instance, are often tissue-specific and species-specific.

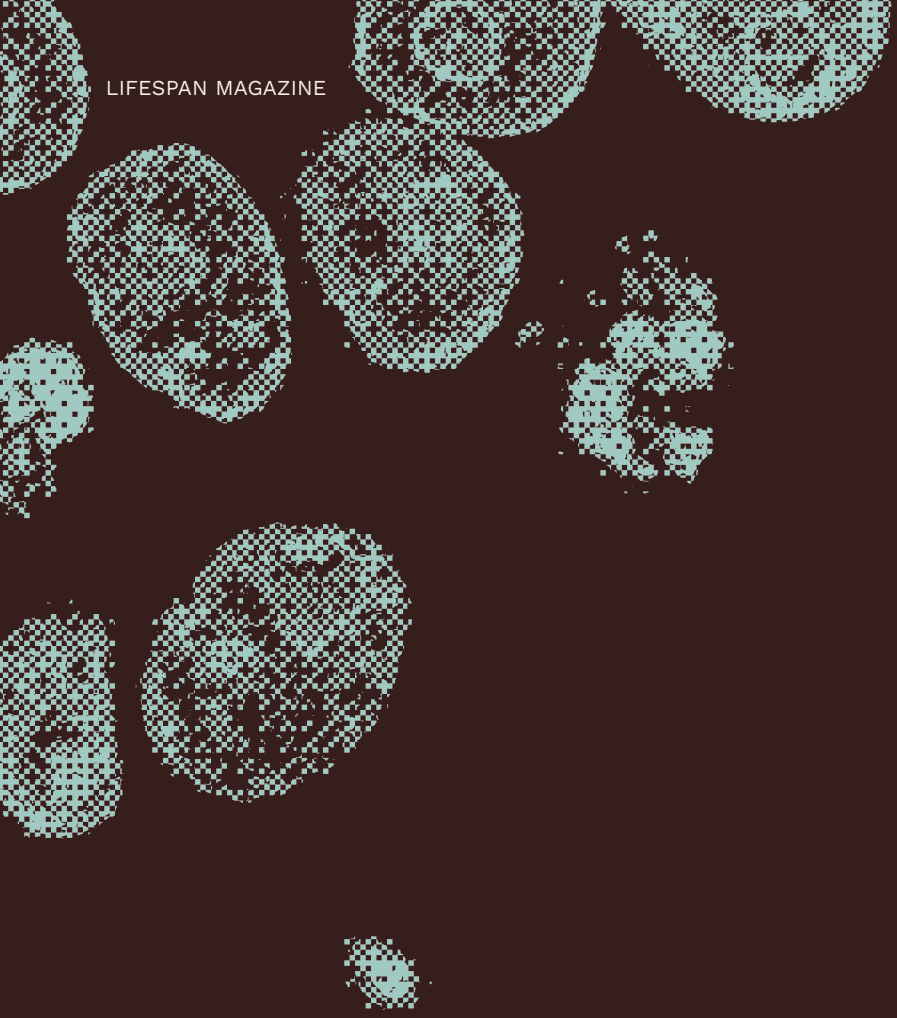
So the picture is nuanced: a core conserved aging program exists alongside enormous species-specific and tissue-specific variation.

5. There are now many different epigenetic clocks out there, and sometimes they don't agree with the same person or intervention. When clocks disagree, how do you interpret that? What do you pay attention to first?

Millions of positions on the DNA molecule change with age, and you can build clocks with very different properties depending on which positions you select and what you train them to predict. Some clocks are designed to be conserved across tissues and species, like the pan-mammalian clocks. Others are tailor-made for a specific cell type, such as human neurons. Clocks can be developed to capture specific facets of aging biology. When two clocks disagree, it usually means they are measuring different things, which is actually informative. The current frontier is building blood-based methylation clocks that reflect the age of specific organs: a blood test that tells you the age of your liver, your kidneys, or your lungs. Rigorous clinical testing will determine which of these clocks ends up being genuinely useful in the clinic. A lot of work remains but I can see the promised land very clearly.

6. If you could correct one common misconception the public has about aging, what would it be?

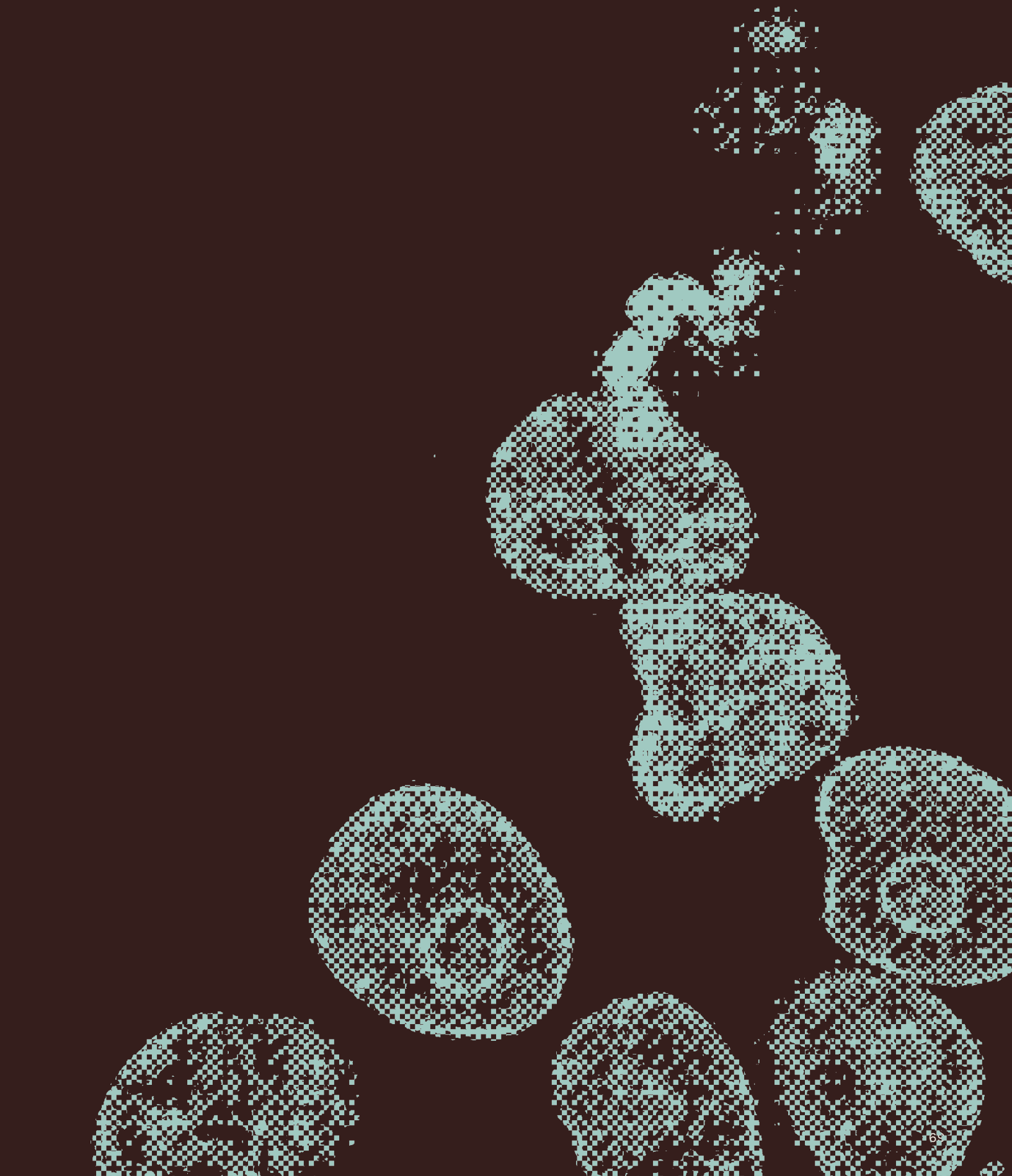
That aging is something we just have to accept. For most of human history, that was true. We had no way to even measure aging precisely, let alone intervene. But now we can measure it, and measuring is always the first step toward changing something. The aging biomarker community builds better and better aging clocks. I have watched the field go from skepticism about epigenetic clocks to serious drug development programs in barely a decade. We are not helpless in the face of aging anymore. That, to me, is the most exciting thing happening in science right now. It is more hopeful than accepting the status quo and the inevitability of aging.



DOGS MAY IMPROVE CANCER SURVIVAL

BY DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: NATIONAL CANCER INSTITUTE VIA UNSPLASH



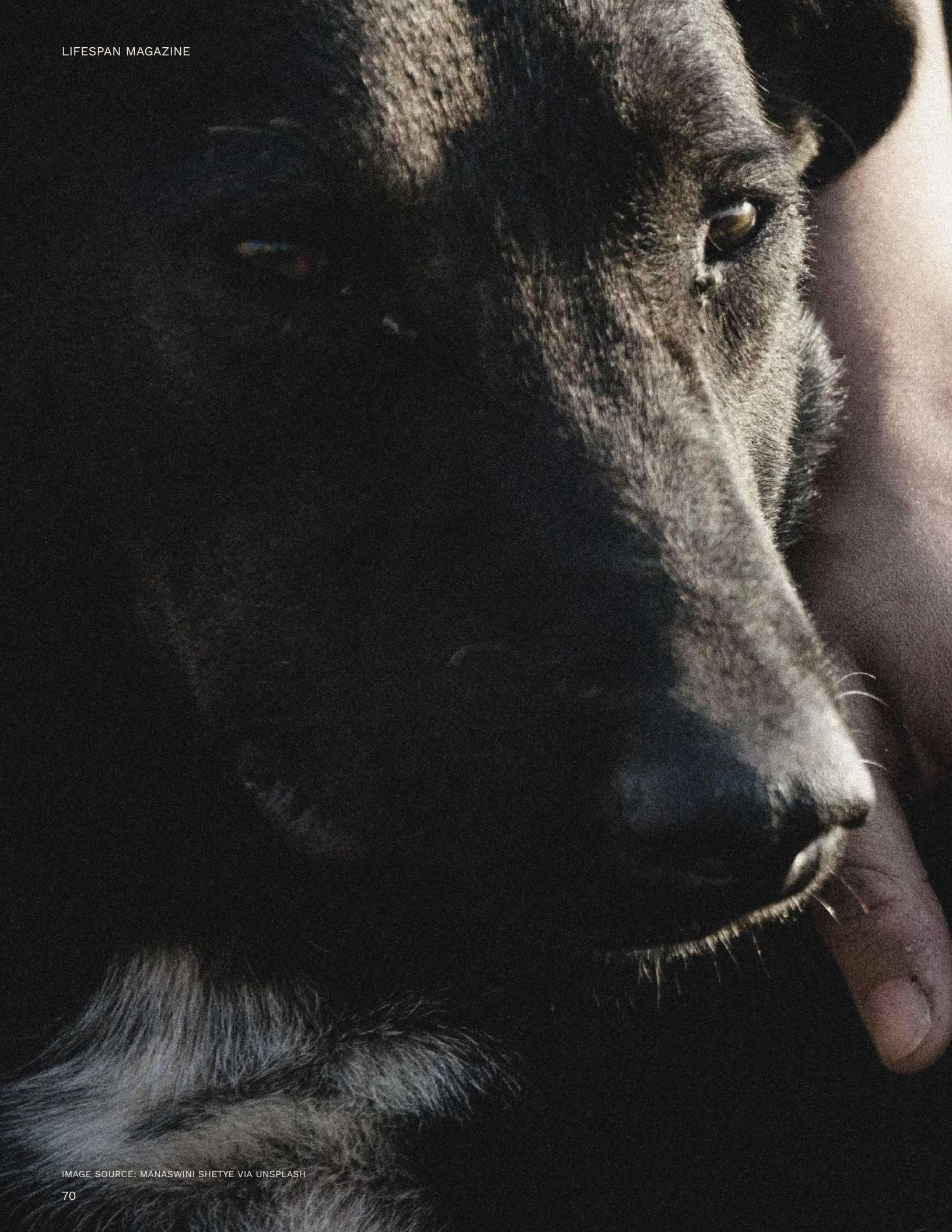
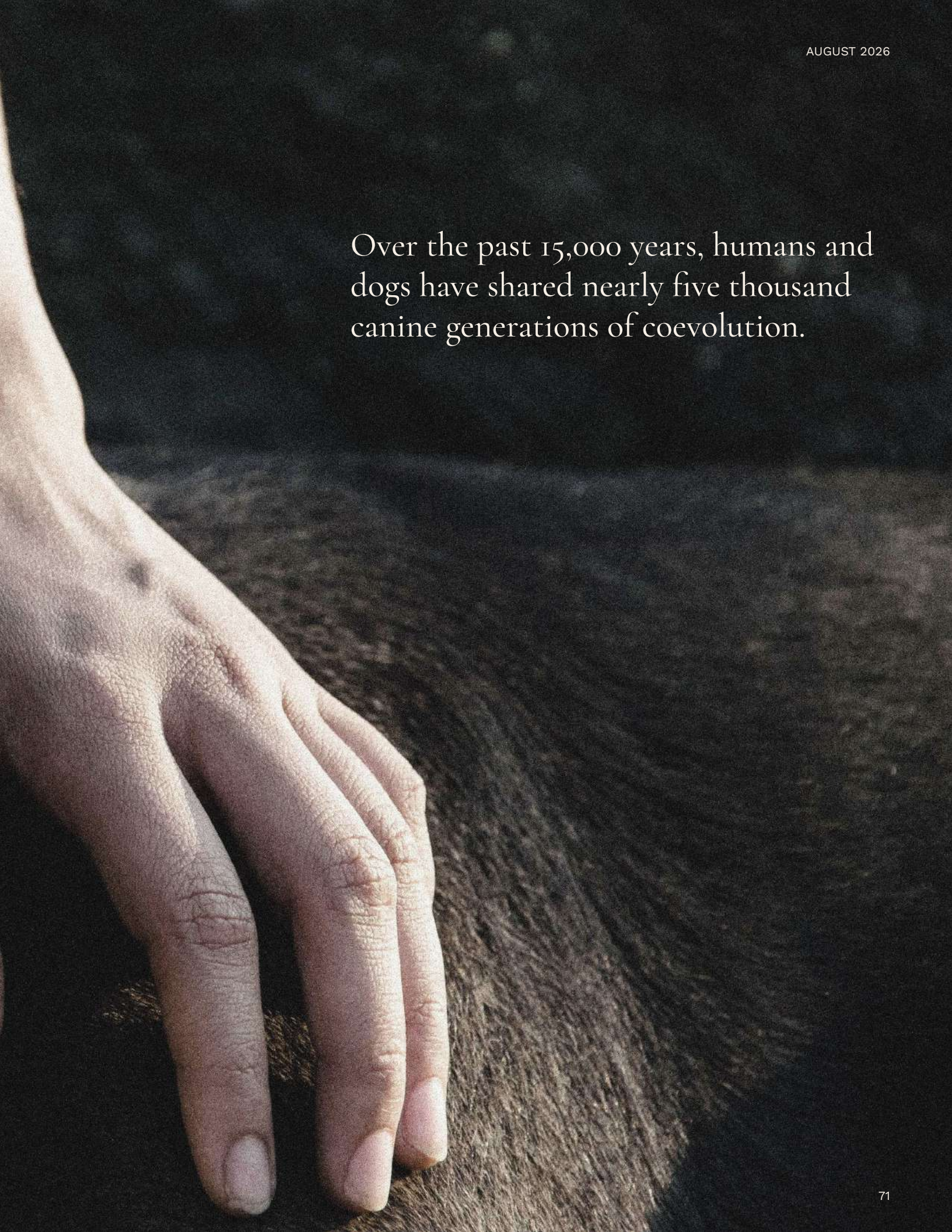


IMAGE SOURCE: MANASWINI SHETYE VIA UNSPLASH



Over the past 15,000 years, humans and dogs have shared nearly five thousand canine generations of coevolution.

Over the past 15,000 years, humans and dogs have shared nearly five thousand canine generations of coevolution. That's enough to change an animal from a predator you fear to a fluffy animal you can carry in your hand luggage.

It's easy to imagine how this started. Wolves that tolerated early human camps gained food and protection, and gradually evolved into dogs exquisitely tuned to us, capable of following our gaze, reading our gestures, and even interpreting our expressions.

A new medical study suggests that this ancient relationship may still influence our biology.[1]

On February 17th, 2026, researchers at the Freie Universität and Charité - Universitätsmedizin Berlin published a study in *Scientific Reports* examining the medical records of cancer patients and asking a simple question: do people who have contact with dogs live longer after a cancer diagnosis?

To answer it, the team analyzed electronic health records from a global clinical network containing more than six million cancer patients. That's a considerable number that allows for strong statistical analysis. Researchers identified individuals with documented dog exposure and compared them with patients without such contact. After carefully matching the two groups for age and sex, the final analysis included 27,631 patients in each group.

The results were striking.

Within five years of diagnosis, about 9.6% of those without dogs had died compared to 4.2% with dog exposure. Statistically, that corresponds to roughly a 56% lower risk of death. When the researchers modeled survival over time, the association appeared even stronger, equivalent to about a 64% relative reduction in mortality risk.

Dogs are obviously not a cancer therapy, and the authors are careful not to claim causation. But the signal is large enough to make scientists wonder what biological forces might be at work.

One plausible explanation is surprisingly simple. Dogs get people moving. Physical activity is one of the most consistent lifestyle factors associated with improved cancer survival. Even moderate daily activity can reduce inflammation, improve insulin sensitivity, and strengthen immune surveillance against tumors.

Dogs may also influence something less obvious: stress. A cancer diagnosis often brings anxiety, depression, and social isolation, all of which are associated with worse outcomes. Interaction with animals has been shown to lower cortisol levels and increase oxytocin signaling, reducing the chronic stress responses that suppress immune function. Companion animals also act as social bridges, prompting interactions with neighbors and strangers that help reduce isolation.

There may even be a microbial component. Humans and dogs share living spaces and microbes,

IMAGE DESIGN BY DR. DAVID A. SINCLAIR, AO, PHD VIA GEMINI

and close contact alters the bacterial communities living on our skin and in our intestines. Some studies suggest that dog owners carry higher levels of beneficial gut bacteria associated with immune regulation and lower inflammation. Since the microbiome can influence cancer progression and response to therapy, these microbial exchanges could help fight cancer.

Still, caution is warranted here. The study relied on medical records, and dog exposure was inferred from diagnostic codes documenting dog contact. Important factors such as cancer stage, treatment differences, smoking status, and socioeconomic conditions were not fully captured. Healthier patients may simply be more capable of caring for a dog. The study identifies a strong association, but it cannot ever prove cause and effect.

Even so, the findings point to something that modern medicine often overlooks: Health is not shaped only by drugs and surgeries. It is also influenced by movement, companionship, and the ecosystems of microbes that surround us and live within us.

For thousands of years humans and dogs have shared campsites, hunts and farms – and more recently our homes and beds. This study suggests that our oldest partnership may still be doing what it has always done: making human lives better for longer.

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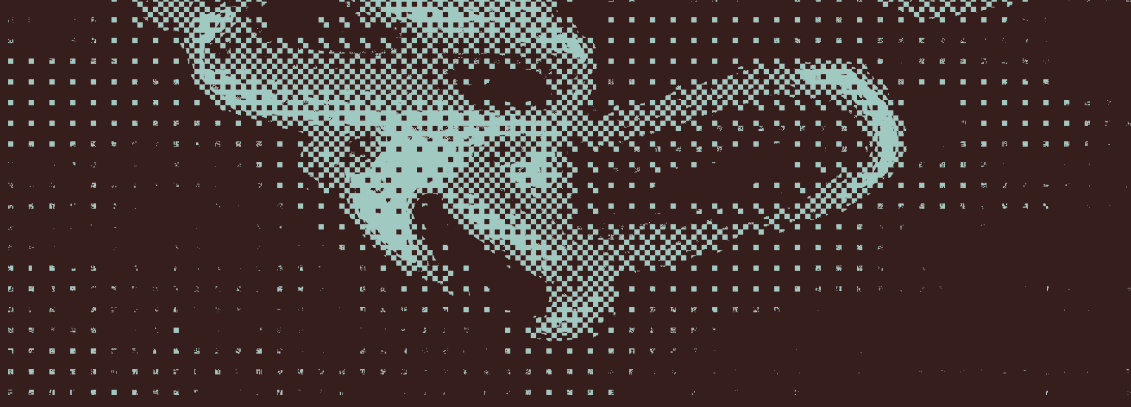
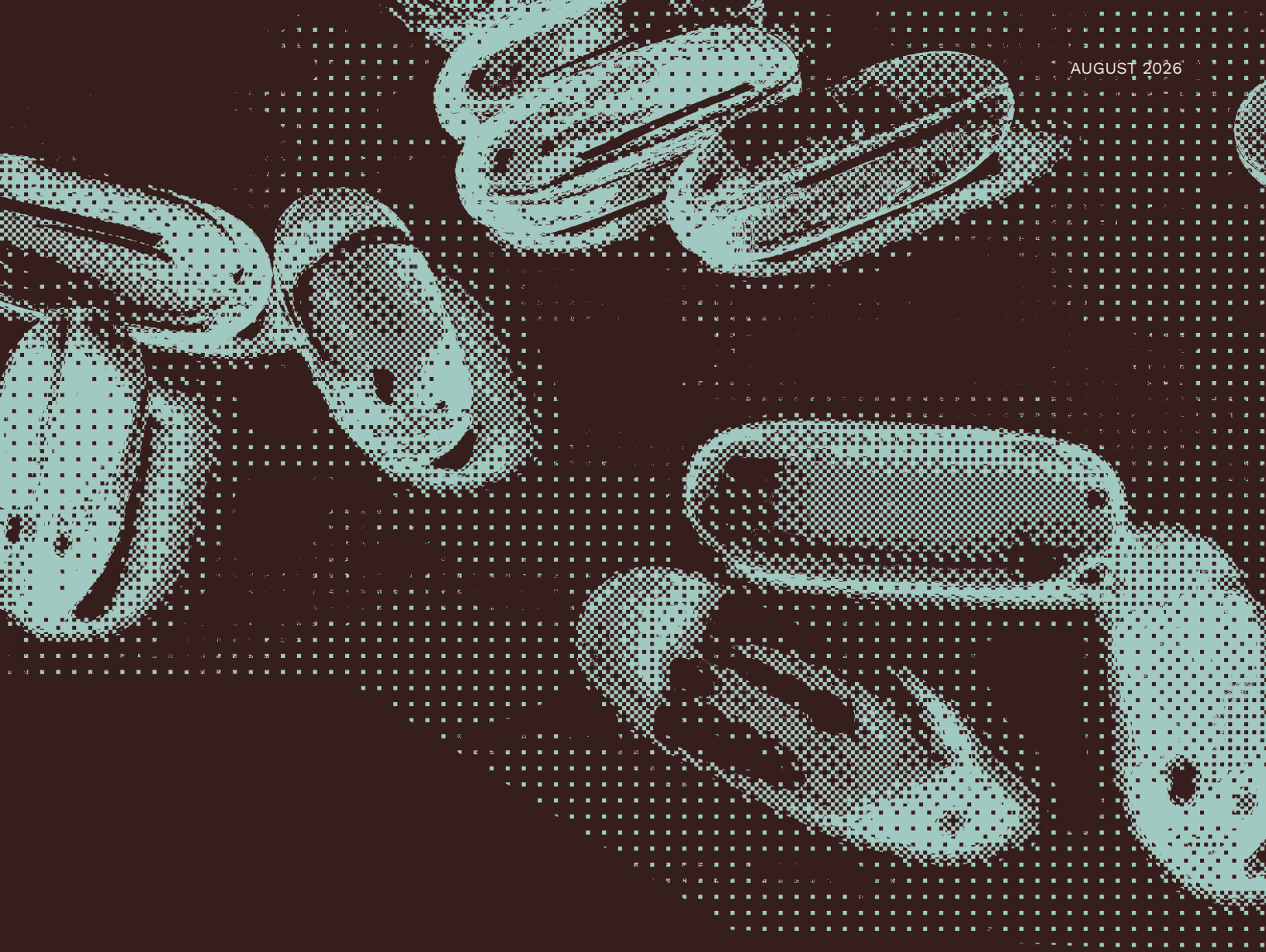


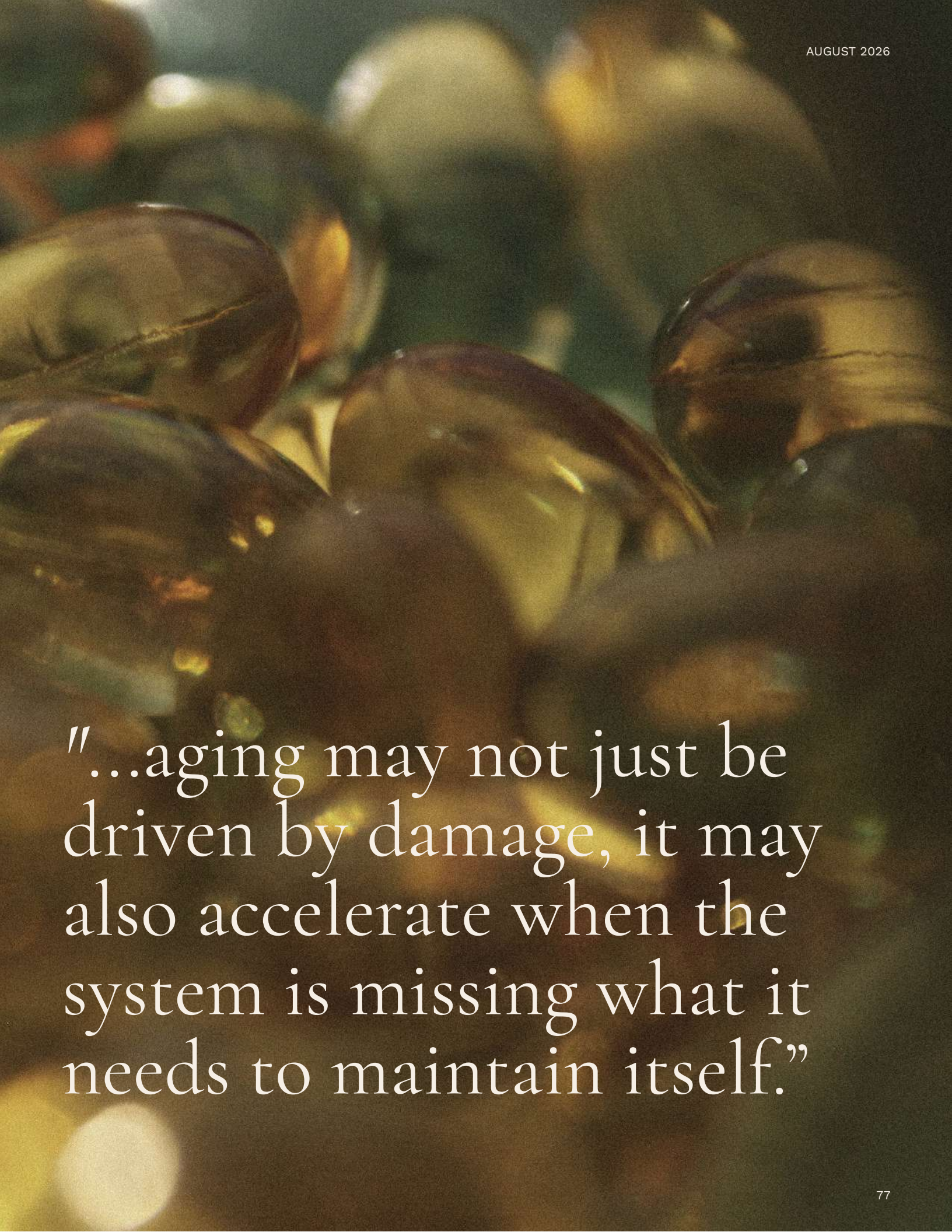
CAN A SIMPLE MULTIVITAMIN MINERAL SUPPLEMENT

IMAGE: NICOLAS SOLERIEU VIA UNSPLASH



SLOW DOWN AGING?

BY ADIV JOHNSON, PHD



"...aging may not just be driven by damage, it may also accelerate when the system is missing what it needs to maintain itself."

You've probably heard the debate about whether taking a daily multivitamin is a good idea. I've had this conversation countless times, and I'll admit I've changed my mind more than once. I might have to change it again, given a recent randomized trial testing whether a regular daily multivitamin affects the rate of epigenetic aging.[1]

On paper, the argument against them is straightforward: if you eat a balanced, minimally processed diet, you should get everything you need. In an ideal world, that's true. But we don't live in that world.

There has been some recent research indicating that more than five billion people worldwide do not have adequate levels of certain micronutrients.[2] In America, most people derive a huge portion of their daily intake of calories from ultra-processed foods. While ideally this would change to a diet that is focused on whole, minimally processed foods, this is not currently the case.

Part of the reason the question about the worth of a daily vitamin keeps resurfacing is that our understanding of vitamins is still relatively recent. Just over a century ago, we didn't even know they existed. Diseases like scurvy and beriberi were common and often fatal, with no clear cause, until Dr. Casimir Funk proposed in 1912 that missing dietary factors or "vitamines" were responsible. Even today, it's easy to underestimate how important these molecules really are.

Vitamin B12 is needed in tiny amounts, yet deficiency leads to neurological damage. Vitamin D regulates hundreds of genes. Vitamin K plays a role in calcium distribution. These are not marginal effects. They are central to basic physiology.

Now to the study.[1] A randomized, double-blind, placebo-controlled clinical trial at Harvard Medical School and Brigham and Women's Hospital in 958 older adults tested whether a daily multivitamin could influence indicators of biological aging, measured using clocks based on DNA methylation. If you're interested in learning more about these biomarkers, check out the interview with Dr. Steve Horvath – the scientist that coined the term "epigenetic clock" – in *this issue*.

The intervention was Centrum Silver, a standard over-the-counter multivitamin that provides a broad mix of essential vitamins and minerals, at standard nutritional levels intended to prevent deficiency rather than enhance physiology.

After two years, participants taking the multivitamin showed a small but statistically significant slowing in two of the five epigenetic clocks assessed, including those previously shown to be associated with mortality risk in older populations.

The magnitude of the effect was modest: roughly equivalent to a few months' difference in epigenetic aging over the two-year period.

That finding is interesting, but it needs to be interpreted carefully. Epigenetic clocks are surrogate markers. They correlate with aging and mortality, but they are not direct measures of lifespan or healthspan, and whether shifting them leads to better outcomes remains uncertain.

The effect was also selective, appearing in some clocks but not others, and the follow-up period was relatively short for studying a process as complex as aging.

Another important detail is who benefited most. Participants who were epigenetically older at baseline appeared to show greater changes, suggesting the effect may be stronger in those aging faster epigenetically.

Step back, and what this study really tested was something quite simple. Not a new drug. Not a targeted intervention. But whether meeting a broad set of basic nutritional requirements could influence measurable features of aging biology. In this trial, it did – modestly, and under specific conditions.

So what can we conclude? According to the study's corresponding author, Dr. Howard Sesso, "Our finding from the COSMOS trial that older adults who take a daily multivitamin for 2 years may improve biological aging by about 4 months as measured by 2 specific epigenetic clocks, with stronger effects among those with more accelerated biological aging at baseline, highlights how randomized clinical trials testing achievable interventions may improve healthy aging. More research is needed to understand how improvements in biological aging translate to tangible health outcomes."

While this study doesn't prove that multivitamins slow actual aging, and the effect was not large, the result suggests that, in at least some individuals, certain aging biomarkers are sensitive to relatively simple changes in micronutrient status.

Despite its limitations, this study may point to something deeper: aging may not just be driven by damage, it may also accelerate when the system is missing what it needs to maintain itself. And if that's true, then part of slowing aging might be surprisingly simple – ensuring that nothing is missing.

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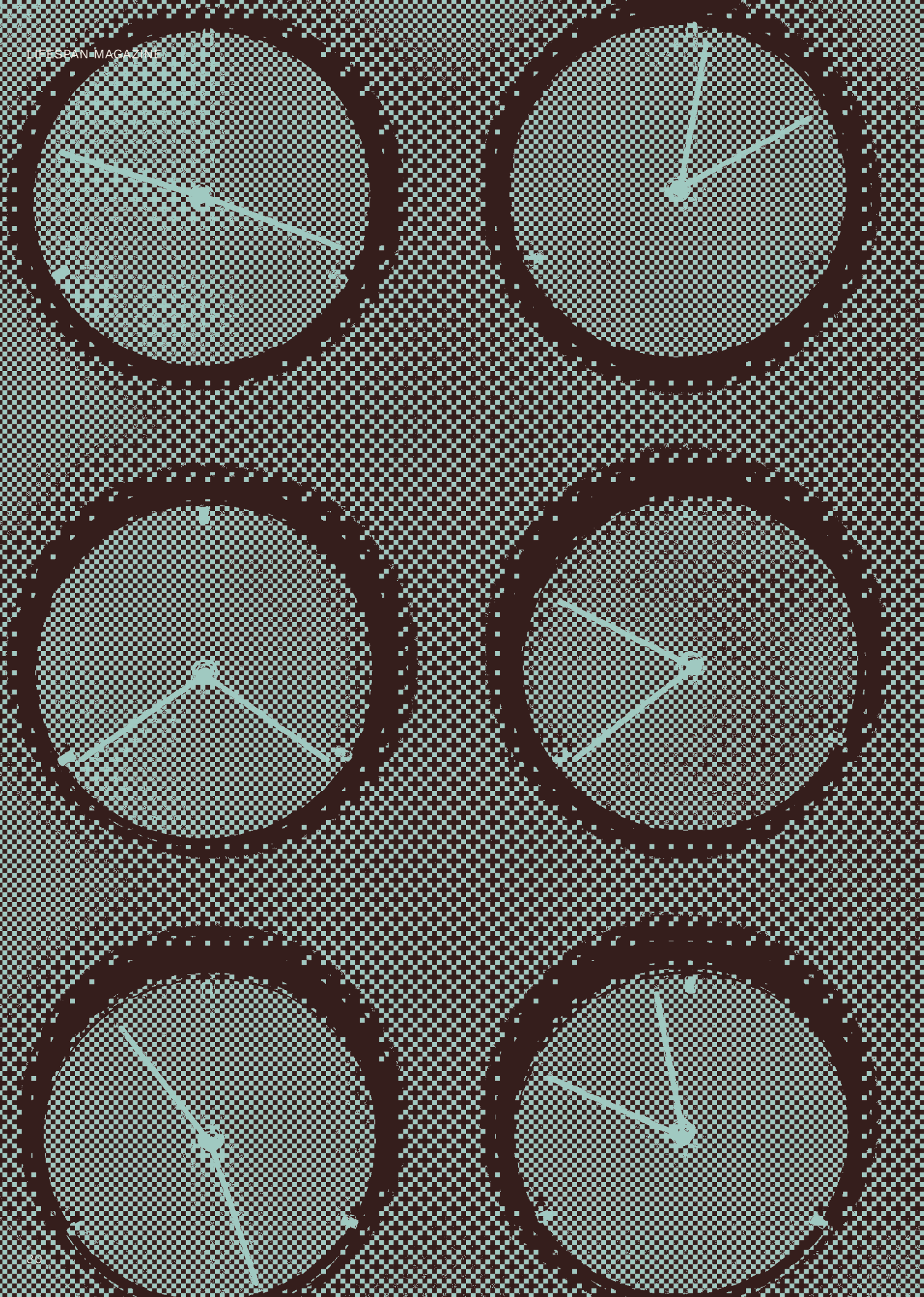

THE MASTER CLOCK OF CLOCKS

BY DAVID A. SINCLAIR, AO, PHD AND ADIV JOHNSON, PHD

IMAGE SOURCE: DONALD WU VIA UNSPLASH

A tiny timekeeper in the brain

There are two clocks in the body. One resets every morning with the rising sun. The other does not reset at all. It accumulates, recording the passage of years.

For the past 20 years, these two systems have been studied separately. Increasingly, however, scientists are finding that they are connected: as we age, the daily clock is disrupted, making it harder to sleep well. Evidence now suggests that the converse is true: if you slow the daily clock, the aging clock may slow too.

Deep within the brain sits a structure no larger than a grain of rice that quietly governs one of the most fundamental features of life: time. This structure, the suprachiasmatic nucleus (SCN), acts as the body's master circadian clock. A bundle of approximately 20,000 neurons located in the hypothalamus, an almond-sized structure deep in the center of the brain, the SCN receives light information originating from the eyes and uses it to synchronize rhythms across the body. Nearly every cell has its own internal clock, and, without the SCN, they drift out of sync.

The importance of this tiny region became clear in 1972 through a pair of remarkable experiments.[1,2] At the University of Chicago, neuroscientist Dr. Robert Moore and his colleague Dr. Victor Eichler set out to test whether a specific part of the brain controlled daily rhythms. To do this, Dr. Moore selectively destroyed a small, little-understood region of the hypothalamus. The animals did not become inactive or sick. They simply lost their sense of time. Hormone rhythms flattened, and the normal daily cycle disappeared. At nearly the same time, Dr. Friedrich Stephan and Dr. Irving Zucker lesioned this region in rats, showing that circadian patterns of drinking and movement were abolished.

What made these experiments powerful was their simplicity. Two independent groups, using different readouts, arrived at the same conclusion: destroy this tiny cluster of neurons, and biological time itself unravels. That cluster would soon be named the suprachiasmatic nucleus: the brain's master clock.

Over the past two decades, a consistent picture has emerged: the circadian system is not just a regulator of sleep, but appears to be a determinant of how fast organisms age. Sleep-like states have been observed in many different organisms.[3] This includes animals as simple as fruit flies, worms, and even jellyfish and hydra, which lack a centralized brain altogether. These animals still enter periods of reduced activity, respond more slowly to stimuli, and compensate with rebound sleep when deprived.

This pushes the origin of sleep back more than 600 million years, to some of the earliest multicellular life. Studies in hydra and jellyfish suggest that sleep-like behavior emerged before the evolution of a centralized nervous system, implying that the need for sleep predates the brain itself. Sleep, in this sense, is not something the brain invented; it is something the brain inherited.

Given its strong evolutionary roots, it's perhaps unsurprising that the consequences of a lack of sleep are not subtle. In a landmark experiment, Dr. Allan Rechtschaffen and colleagues subjected rats to sleep deprivation.[4] At the time, it actually wasn't clear if sleep was even totally necessary for normal physiological function. The results were striking and tragic: the experimental rats unable to sleep exhibited major health problems, suffered

from severe pathology, and ultimately experienced early death.

A similar effect happens when the underlying clock is disrupted directly. In mice, altering key circadian genes accelerates aging.[5] And in humans, chronic circadian misalignment, as seen in shift work or irregular sleep, is strongly linked to a variety of chronic diseases.[6]

Circadian rhythms and longevity

Circadian rhythms, it turns out, might matter as much as what we eat. In mice, aligning feeding with the natural circadian cycle while maintaining a daily fasting period extends lifespan by up to 35%, beyond what 30% caloric restriction alone could achieve.[7] Even in simpler organisms, including fruit flies, manipulating the circadian clock alters lifespan,[8] suggesting that the relationship between timekeeping and aging is deeply conserved.

None of this is surprising when viewed through a broader lens. Sleep, one of the most visible outputs of the circadian system, remains one of the strongest predictors of health and longevity. Both insufficient and excessive sleep are well known to be associated with increased mortality risk, hinting that the underlying issue is not just duration, but the integrity of the biological clock itself.

If sleep reflects the health of the circadian system, the next question is whether this system can be improved.

In a recent issue of *Cell*, Dr. Eric Zhang and colleagues published an elegant study that set out to do just that.[9] They started with a human cell line engineered to report circadian activity, then screened thousands of compounds that amplified what scientists call circadian amplitude, a measure of how robust the clock's oscillations are. They identified one that worked well: 3′-deoxyadenosine (3DA), or cordycepin, a bioactive compound found in the orange parasitic fungus *Cordyceps militaris*.

The effects of 3DA extended beyond cell culture. In mice, the compound improved metabolic health, reduced inflammation and DNA damage, enhanced muscle function, and, most notably, extended lifespan by approximately 12%. The benefits were time-dependent, and the authors ultimately settled on a dosing schedule of three times per week: Monday, Wednesday, and Friday.

3DA also appeared to influence multiple hallmarks of aging simultaneously and reduced epigenetic age, a more contemporary aging biomarker based on DNA methylation. Epigenetic aging clocks were pioneered by Dr. Steve Horvath (check out the interview with Dr. Horvath in this issue). Well-designed clocks are not only strongly correlated with chronological age but are significantly associated with future age-related outcomes, including all-cause mortality.

One fascinating aspect of the study is that 3DA influences a specific region of the brain called the paraventricular nucleus (PVN). Within the hypothalamus, the SCN and the PVN are closely connected neighbors. While the SCN is the master clock that generates the 24-hour rhythm, the PVN acts as the primary effector. It is effectively the relay station that receives this timing signal and coordinates the body's hormonal, metabolic, and autonomic outputs.

Study limitations and additional questions

Important questions remain. For example, the study was conducted in male mice, leaving open whether the same effects extend to females. Translation to longer-lived species, including primates, may also be essential before clinical applications can be considered. Still, the significance of the work lies less in the molecule itself than in what it reveals. It suggests that the biological clock of aging may be governed, at least in part, by the daily circadian clock.

These changes are not independent effects but likely arise from a shared mechanism. The circadian system operates through epigenetic control of gene expression, regulating when genes are turned on and off across the genome. As these rhythms weaken with age, gene expression becomes less coordinated, and cells lose access to the information that once maintained their identity and function. Seen in this light, aging appears partially due to a gradual loss of timing that can be potentially restored.

If these findings hold, they suggest a shift in how aging might be slowed. Rather than targeting individual pathways, it may be possible to intervene at the level where biological processes are coordinated. Medicines could act not only on cells, but on the timing that governs them, restoring coherence across systems rather than repairing them one by one.

This returns us to the original distinction between the clocks. The clock that governs the day and the clock that governs a lifetime may not be separate systems, but different expressions of the same underlying biology. So, if aging truly reflects a breakdown of that timing system, then one of the most effective ways to slow the aging clock may simply be to enhance the daily one.

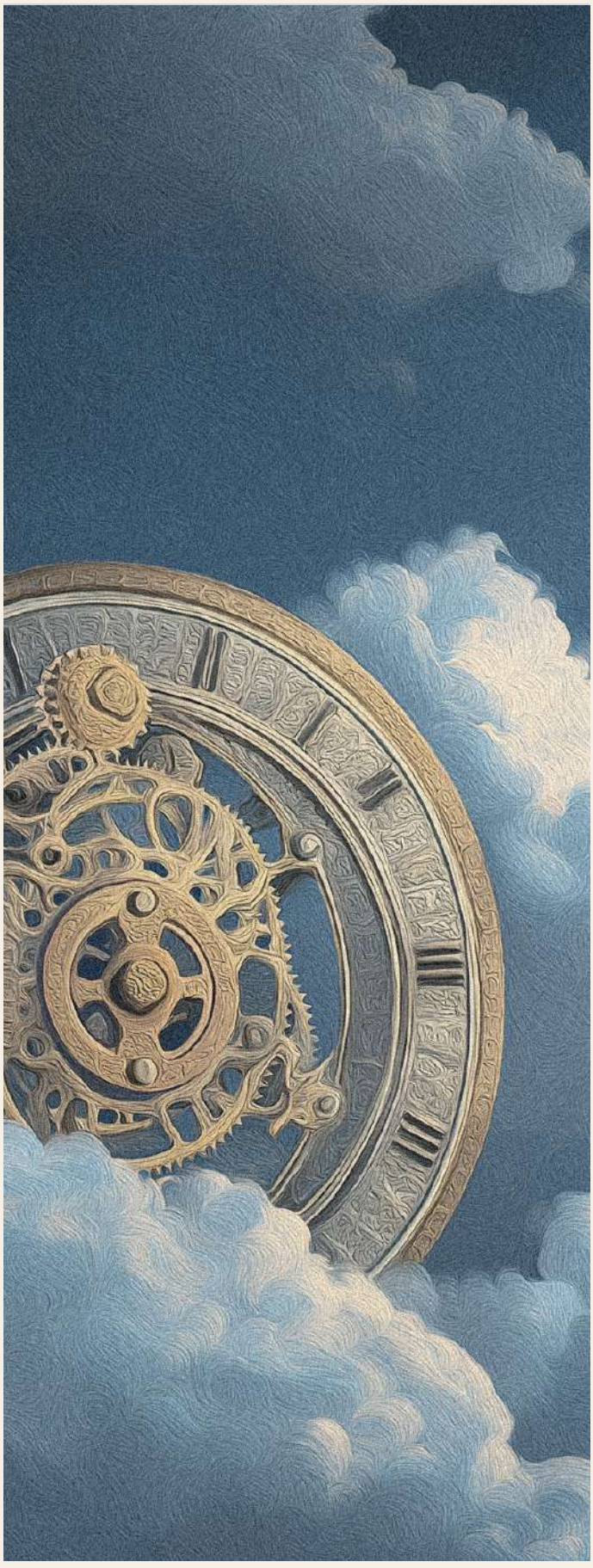

IMAGE SOURCE: MIDJOURNEY.

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OPINION

CAN OVERUSING AI IMPAIR YOUR COGNITION?

BY ADIV JOHNSON, PHD

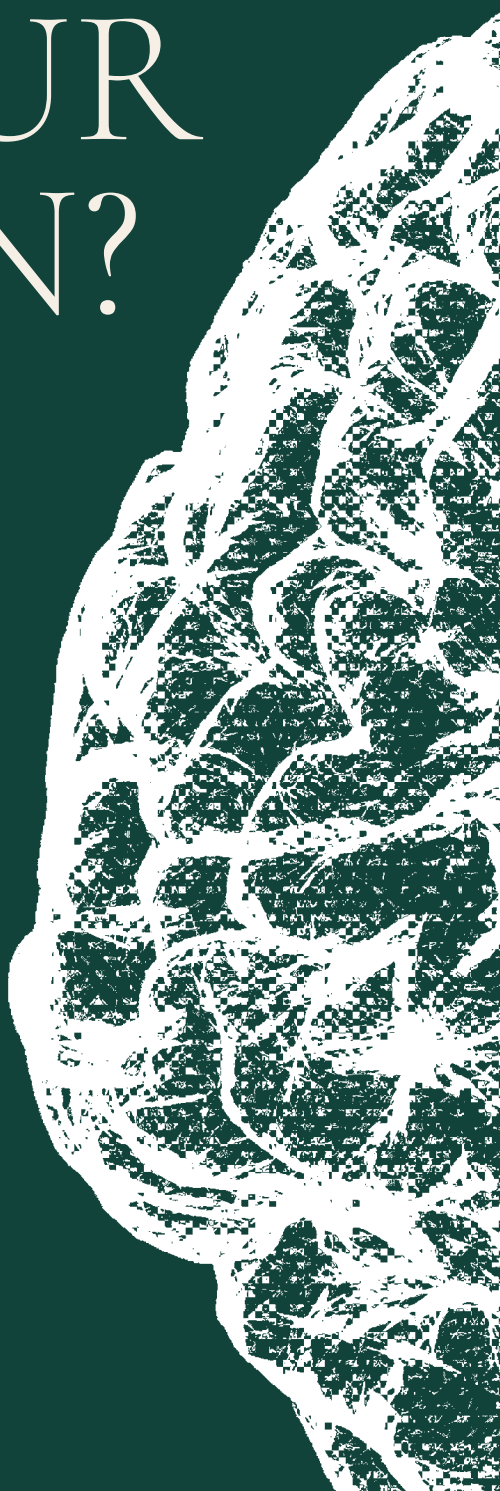
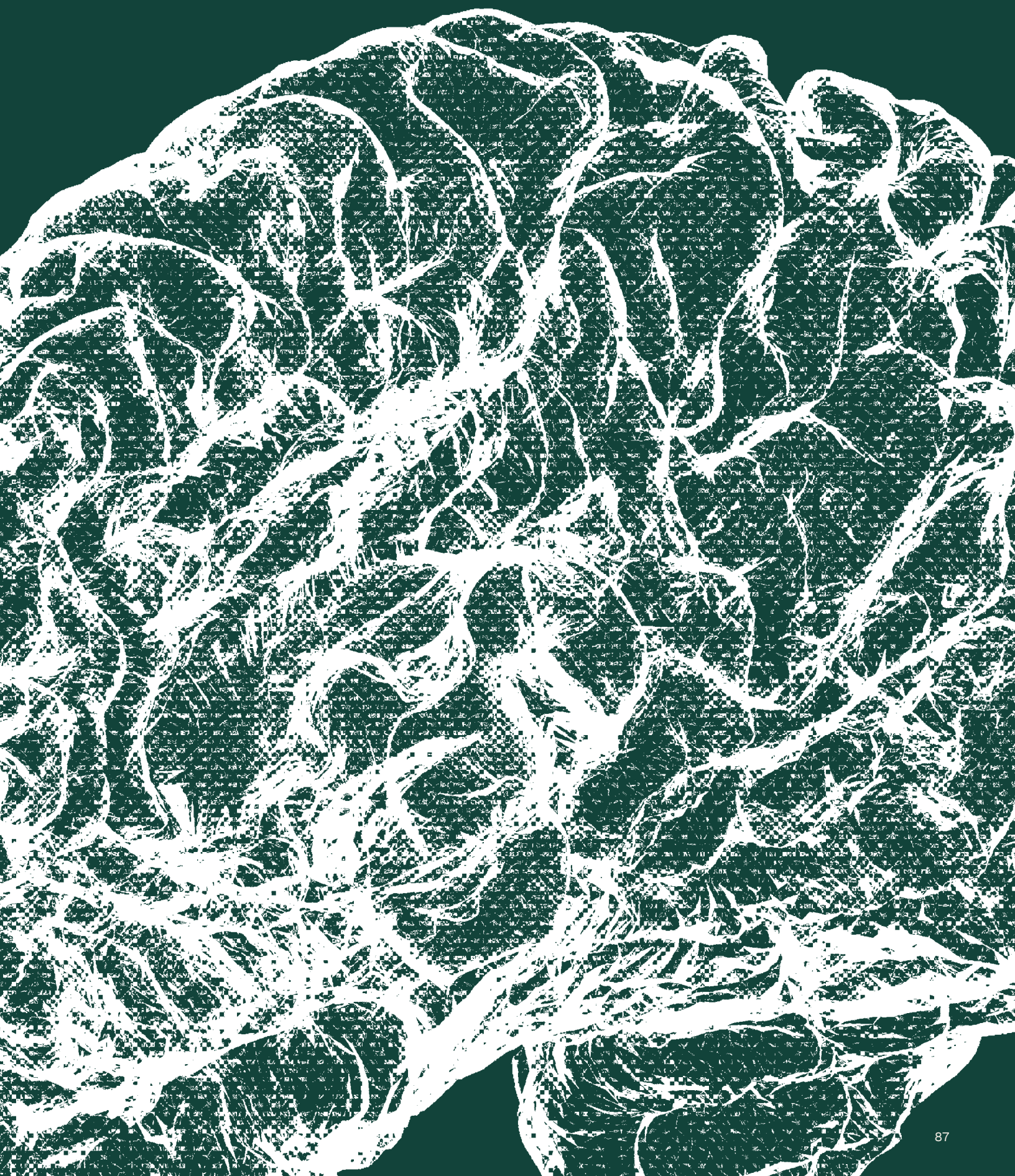


IMAGE SOURCE: SHAWN DAY VIA UNSPLASH



The headlines for artificial intelligence (AI) have been outrageously sensational since the advent of OpenAI's ChatGPT in November of 2022. Some headlines represent classical "doomer" perspectives and argue that societies are on the verge of colossal job loss or are about to be taken over by ruthless, sentient robots. Others are passionately optimistic and predict that sci-fi-style discoveries are just around the corner that will revolutionize health, aging, space travel, and more.

There's a good chance that you, the reader, have been using AI more and more in different ways. Maybe you've worked with a large language model (LLM) to help design a travel itinerary or suggest restaurant recommendations for a fun night out with friends. As someone who loves to cook, I've found AI quite useful for whipping up new recipes or coming up with suggestions for how to spice up a certain dish. Recently, generative AI gave me helpful advice for how to make a whole grain-based pizza crust at home. In case you're curious, increasing the amount of water is key when working with whole wheat flour.

While using AI to help you make a healthier pizza seems pretty innocuous, an emerging body of data suggests that overusing AI can degrade our ability to think. As we increasingly offload everyday judgement and problem-solving to AI, we may be quietly training our brains to do less heavy lifting.[1] If that shift becomes widespread and long-lasting, the loss to our collective cognitive capacity could be substantial.

Rapid rise and adoption of LLMs

The use of AI has become progressively more ubiquitous. According to a Pew Research Center poll from September 2025, 62% of adults within the United States reported interfacing with AI several times a week or more and 73% expressed comfort with AI assisting them at least a little bit on a daily basis. Despite this widespread usage, 53% of Americans believe that AI will worsen people's ability to creatively think and 50% say that AI will hinder the ability of people to establish meaningful relationships.[2]

Broadly speaking, the use of AI has been associated with a loss in cognitive power. For example, one 2025 paper published in the journal *Societies* presents findings from interviews and surveys with more than 600 individuals.[3] Not only was the frequent use of AI tools significantly correlated with a reduction in critical thinking ability, but younger adults were more dependent on AI tools and displayed reduced critical thinking scores relative to older subjects. A separate questionnaire-based study involving 206 university students concluded that AI represents a real, perceived threat to both critical thinking and student retention.[4] Distinct survey-based research published in *Annals of Neurosciences* concluded that the long-term use of AI in adults was significantly associated with information overload, mental exhaustion, and attention strain. People who engaged in long-term AI use were also more likely to have less self-confidence when it came to decision-making.[5]

Research has also found that people have an inflated sense of how accurate LLM models are. The longer the explanation provided by the chatbot, the more confident users are in the validity of the response. The difference between how much confidence an LLM has in its own answer and human

confidence in that response is known as the calibration gap. A separate divide — how well humans and AI can differentiate between true and false answers — is known as the discrimination gap.[6]

The negative effects of cognitive outsourcing

Delegating an intellectually challenging task to an LLM model is a type of cognitive outsourcing. Although the evidence is early, there's some interesting research suggesting that cognitive outsourcing may be risky business.

The first example is one that made headlines when it first emerged out of MIT Media Lab.[7] In this elegantly designed study, 54 participants were asked to write an essay using nothing but their brain, their brain and a search engine, or their brain and an LLM. By tracking brain activity via electroencephalography, the researchers found that brain connectivity was weakest in the LLM group. Those who utilized an AI chatbot also had difficulty quoting the work they produced. The authors concluded that LLM use led to behavioral, neural, and linguistic underperformance.

Smartphones are an interesting analogy here. Last year, a fascinating paper emerged in *PNAS Nexus* with the title "Blocking mobile internet on smartphones improves sustained attention, mental health, and subjective well-being."[8] Given personal accounts and correlational evidence that smartphones can impair mental health and cognition, the authors conducted a randomized controlled trial where smartphones were effectively converted into dumbphones. More specifically, an application was used to prevent participants from accessing the internet on their smartphones for two weeks. The results were eye-catching. After a two-week smartphone internet fast, 91% of subjects showed improvements in mental health, the ability to sustain attention, and/or subjective well-being. The improvement in sustained attention ability was approximately equivalent to undoing 10 years of age-related brain decline.

Potential futures

What does the future hold for human and AI interaction? The possibilities range from delightfully optimistic to depressingly dystopian. On the brighter side of the spectrum, humans and AI truly complement each other. The famous inventor Dr. Ray Kurzweil has even predicted that, in the coming years, human intelligence will fully merge with AI.[9] In such a scenario, human cognition is dramatically expanded by artificial neurons. On the darker side of the spectrum, a potential future is imagined where human intellectual capacity is thoroughly degraded by a progressive overreliance on AI.[10] The result is a human species that is far less capable than it is today.

These projections remind me of other, broader conversations happening right now regarding how we collectively relate to technology. Recently, I read two books that deliver sharp critiques of technology: *The Anxious Generation: How the Great Rewiring of Childhood Is Causing an Epidemic of Mental Illness* by Dr. Jonathan Haidt and *Against the Machine: On the Unmaking of Humanity* by Paul Kingsnorth. The first book by Dr. Haidt makes a chilling and compelling case that early exposure to smartphones and social media is corrupting childhood development. Of major concern is the impact of this recent technology on pediatric mental health and attention. The latter book by Kingsnorth makes a much broader, more provocative claim, which is that technological progress since early industrialization has broadly harmed human flourishing.

I'm starting to detect a zeitgeist shift in how we collectively view technology. It's clear that not all technological progress is inherently positive and some recent inventions – particularly social media – are almost certainly a net negative. I'm sensing a growing skepticism of technological progress and emerging research very much gives voice to this instinct. Many parents, including myself, are certainly worried about what the impact of early AI use will be on childhood development.

What to make of the data

While alarming, it's important to realize that this is an area that has not been heavily researched. Correlation does not equal causation and, realistically, more rigorous human trials will be needed to make strong statements. If we take a step back and try to be objective, it's probably too early to draw any firm conclusions.

That all being said, this may be a very real concern. Having generative AI interpret an essay for you is not like reading on a digital tablet instead of printed paper. It's also not like using graphical software to make a complex graph or visual as opposed to drawing it on a poster board. There is something fundamentally different about having an LLM summarize a paper for you so that you don't have to read it yourself.

Reading and related tasks are foundational to human intellect and are some of the best ways to train and grow our minds. There's a reason that our brains consume 20% of bodily energy despite only being ~2% of our body weight – the brain is a metabolically hungry organ that requires immense resources to support its remarkable cognition.

Dr. Cal Newport, a professor of Computer Science at Georgetown University who studies technology, digital ethics, and productivity, previously compared having an AI model handle cognitively challenging tasks to going to the gym with a forklift.[11] Rather than lift the weights yourself using your own muscles, you forfeit all of the expected musculoskeletal, metabolic, and longevity benefits by instead having the forklift lift it for you.

Using AI without losing your edge

There's no doubt that AI models can be extraordinarily useful. The other day, I noticed that something was broken in my backyard. I hadn't the slightest idea what the piece was called at the time and, after taking a picture of it and sharing it with Google Gemini, I immediately learned it was a flexible downspout extension connector. From here, I was able to go online, order a new one, and replace the part once it arrived.

I think this is a good example of how to enjoy the benefits of AI without risking cognitive harm. The only part of this process that involves actual work is replacing the part. There's little to no cognitive work in asking people if they recognize this part and know what it's called. Here, AI is serving as a highly convenient accelerator and time saver.

This type of approach can be easily extended to many other kinds of work. Instead of having AI summarize a paper, essay, or book, AI can be a powerful tool for making sense of challenging terms or concepts. Rather than have AI read the text for you, you can read it yourself and use AI as a guide to answer questions about definitions or terms you don't understand.

Moving forward with caution

Regardless of the specific approach employed, generative AI should be used thoughtfully. Until more is known about the risks, the most prudent path forward is to be careful about offloading cognitively challenging tasks to a chatbot. While AI can be a helpful collaborator that increases throughput and efficiency, it should ideally augment, not replace, your own cognitive effort and critical thinking.

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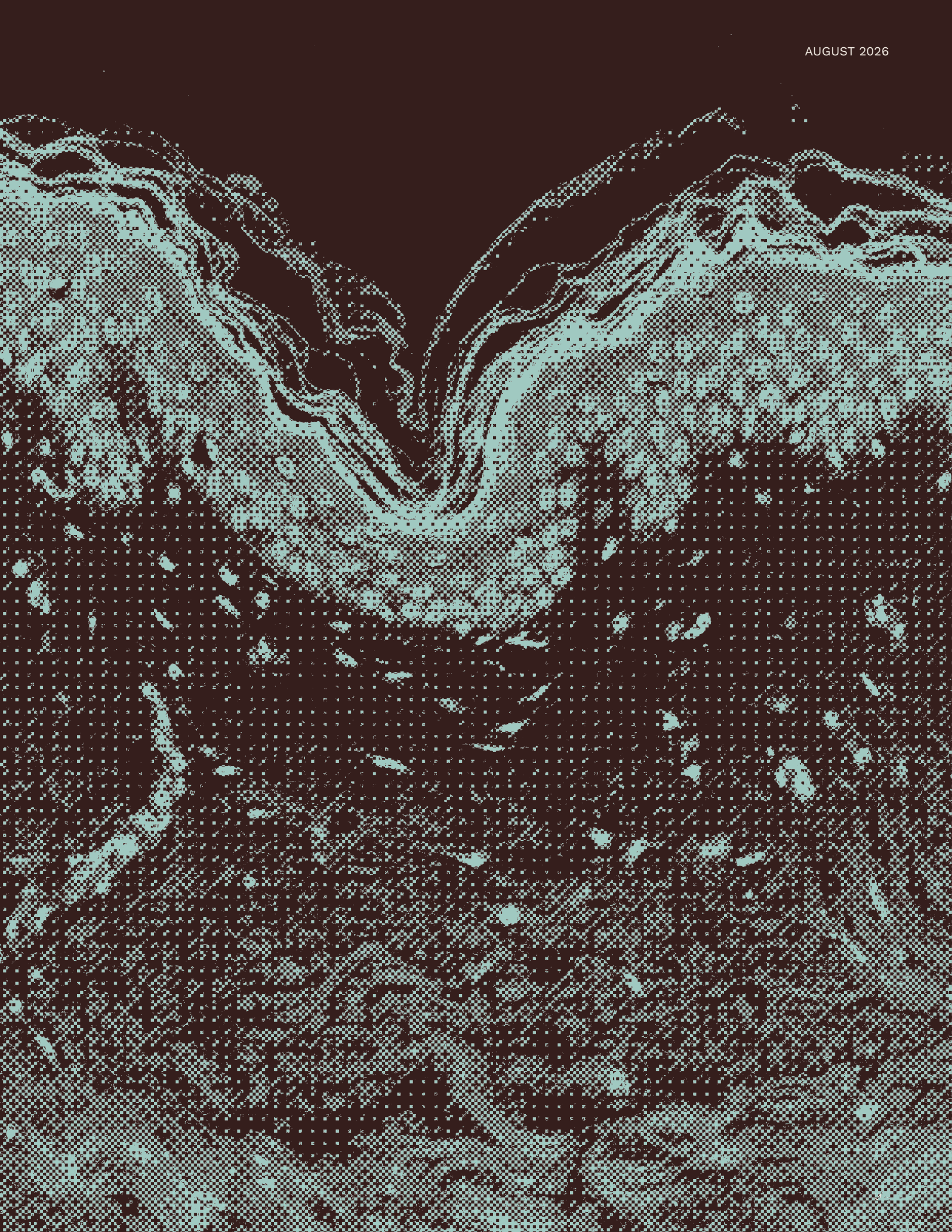
SENOLYTIC TRIAL IN SKIN, WITH BROADER IMPLICATIONS

BY DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: JOSLOUIS VIA ADOBE STOCK

AUGUST 2026



“The study marks a step that the field has been working toward for years: moving from animal models to human testing of therapies that target the underlying biology of aging.”

IMAGE SOURCE: MIDJOURNEY.

A California-based biotechnology company backed by Khosla Ventures has reported preliminary Phase 1 results for its experimental drug RLS-1496, a topical treatment designed to eliminate senescent cells in patients with psoriasis, atopic dermatitis and age-damaged skin.[1] The underlying idea, that removing a class of dysfunctional cells might alter the trajectory of disease, is beginning to be tested, not in theory, but in patients.

The study, conducted in the Netherlands for Rubedo Life Sciences, was small and primarily intended to assess safety. But it was notable for a different reason. The drug is among the first to enter human testing with the explicit aim of targeting senescent cells, a class of dysfunctional cells increasingly implicated in aging and chronic disease.

Rubedo was founded by Marco Quarta, Ph.D., who received his doctorate degree from the University of Bologna and a Ph.D. in Neuroscience from the University of Padua and a post-doc in Aging and Stem cell Biology in the lab of Prof. Thomas Rando at Stanford University. He is also President and co-founder of the scientific organization Phaedon Institute, focused on Longevity Medicine.

“We are excited to reach this important milestone,” the company’s chief executive, Dr. Frederick Beddingfield, said in a statement, adding that the trial would help determine whether the drug has “disease-altering effects” in inflammatory skin conditions and skin aging.

Senescent cells accumulate with age after damage or stress. They do not divide, but they remain metabolically active and secrete inflammatory factors that can disrupt surrounding tissue. Their presence has been linked to a range of conditions, from arthritis to fibrosis and metabolic disease.

For more than a decade, researchers have sought ways to selectively remove these cells. In animal models, clearing them can improve tissue function and, in some cases, extend lifespan. Translating that concept into humans has proved more difficult, in part because of concerns about safety and the challenge of targeting only harmful subsets of senescent cells.

Rubedo’s approach focuses on a protein called GPX4, which regulates a form of cell death known as ferroptosis. The company says its drug selectively targets “pathological senescent cells that drive inflammaging,” a term used to describe chronic, low-grade inflammation associated with aging.

Rubedo's “Alembic Platform” is an AI-driven engine that uses single-cell multi-omics to identify specific "Achilles' heels" in different types of senescent cells across various tissues. Dr. Quarta, the company’s chief scientific officer, described the effort as the culmination of years of work across the field.

“For the last decade, longevity scientists have been working to develop a compound ready for human trials that safely and effectively targets pathologic senescent cells,” Dr. Quarta said.

The choice to begin in skin reflects practical considerations. Topical therapy limits systemic exposure and allows researchers to measure localized biological effects more directly. In this study, investigators assessed not only disease lesions but also adjacent areas of skin to track changes associated with aging.

Still, the broader significance lies less in dermatology than in proof of principle.

What is not stated in the press release, but is well understood within the field, is that the skin is one

of the few human tissues where senescent cells can be directly sampled, mapped and followed over time with minimal risk. That makes it an unusually powerful testing ground.

In recent years, advances in single-cell sequencing and spatial transcriptomics have made it possible to distinguish harmful senescent subpopulations from those that may play beneficial roles in wound healing or tumor suppression. The ability to target only the former, rather than eliminating senescence wholesale, has been a central challenge.

Several groups, including those working with early senolytics such as dasatinib and quercetin, showed that clearing senescent cells in animals could improve function across multiple organs. But those approaches have struggled with specificity and tolerability in humans. More recent efforts have shifted toward what some researchers describe as "precision senolytics," aimed at specific cell types, tissues or signaling pathways.

Rubedo's GPX4 strategy is part of that shift: by sensitizing certain senescent cells to ferroptosis, the company is attempting to exploit a vulnerability that may be more pronounced in diseased or aged tissue than in healthy cells. Whether that selectivity holds in larger human studies remains an open question.

There is also a broader context that is not often discussed outside research circles. Senescent cells are not confined to the skin. They accumulate in adipose tissue, where they influence insulin sensitivity; in the vasculature, where they contribute to stiffness and atherosclerosis; and in the brain, where they have been linked to neuroinflammation. What happens in the skin, biologically, is not isolated. It reflects processes occurring throughout the body.

If senescent cells can be safely reduced in human tissue, even in a localized setting, at least one component of aging biology may be modifiable in patients. The question is whether that effect can be extended beyond the skin. Rubedo has indicated that it is developing systemic versions of the drug and exploring applications in metabolic and fibrotic diseases.

For now, the results remain preliminary, and the trial is not designed to establish efficacy. But the study marks a step that the field has been working toward for years: moving from animal models to human testing of therapies that target the underlying biology of aging.

From my perspective, having watched this field develop over decades, the importance of this moment is not that a skin condition might improve; it's that a long-standing hypothesis is being tested where it matters most. If removing senescent cells proves to be safe and even modestly effective in humans, it would validate the central idea that aging is not simply a passive process, but one that can be intervened upon by targeting specific cellular states.

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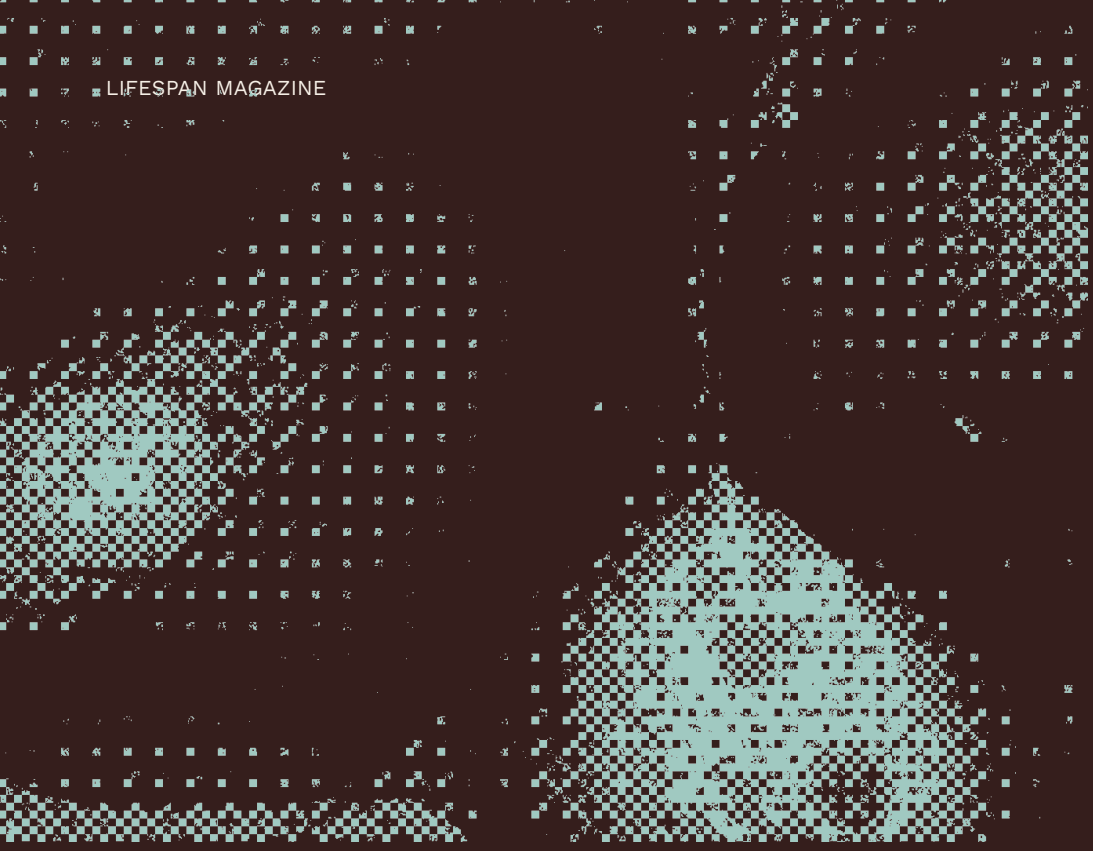
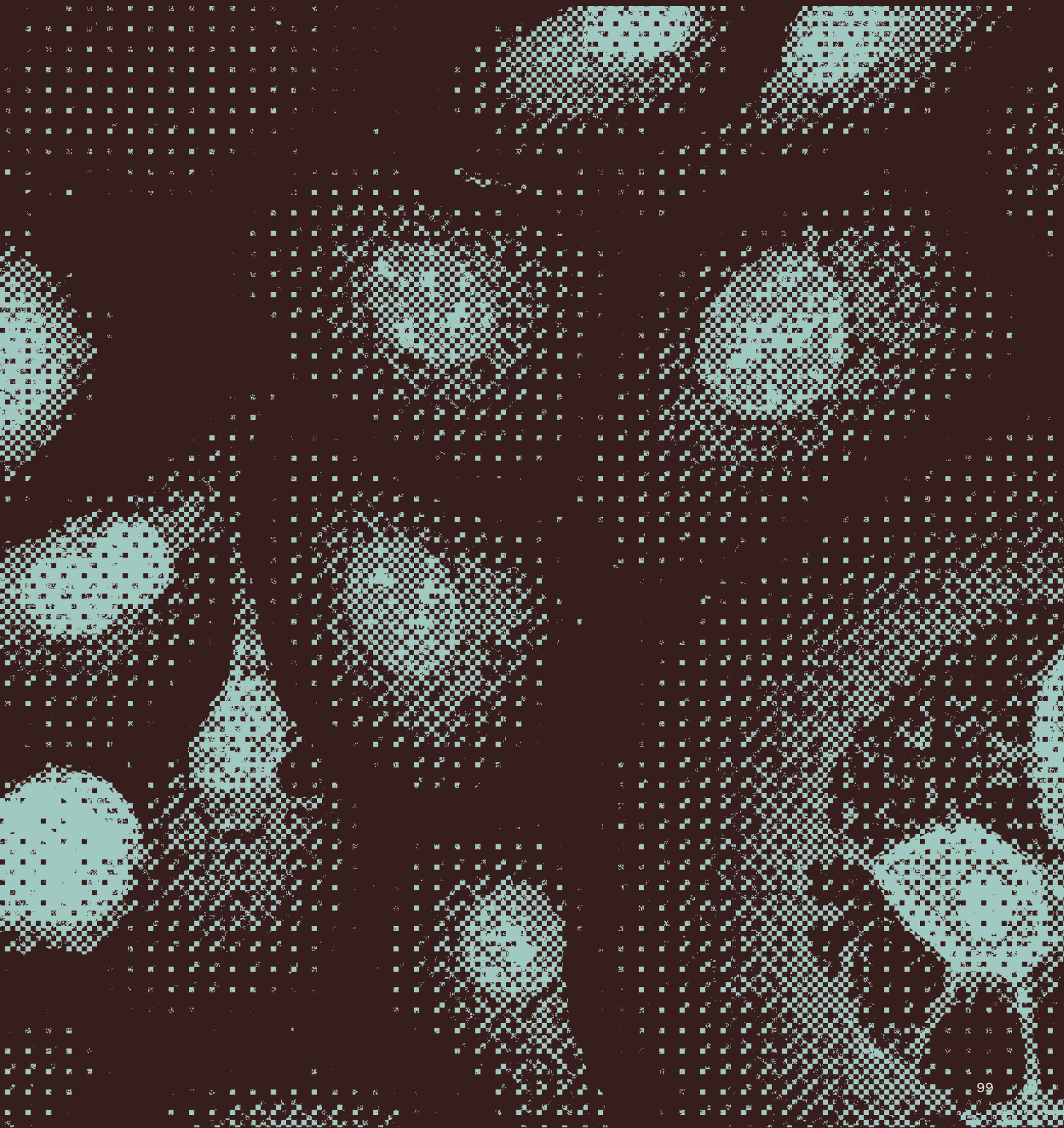


THE THYMUS IS BACK

BY DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: NATIONAL CANCER INSTITUTE VIA UNSPLASH



For decades, the thymus, a small organ tucked behind the breastbone, has been all but forgotten. Long thought to matter only in childhood and fade into irrelevance in adulthood, that assumption is now being challenged. We may be only as young as this part of the immune system we have ignored for too long.

Beginning in adolescence, the thymus does not simply shrink, it is steadily replaced by fat in a process called "involution". By midlife, its production of new T cells has dropped sharply. In later decades, the thymus is small and largely inactive, and the immune system becomes less diverse, more inflammatory, and slower to detect infections and cancer.

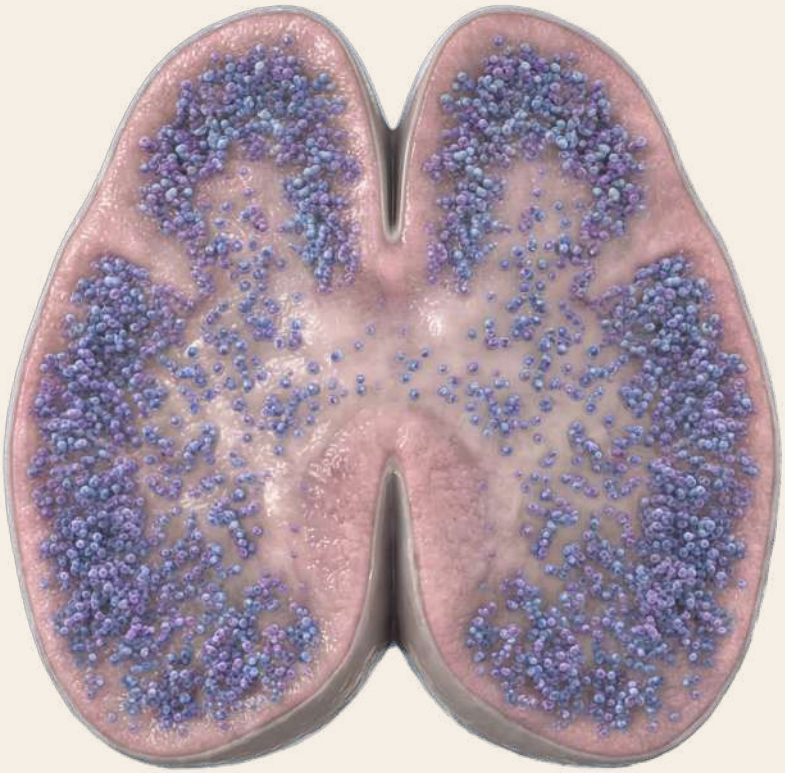
In a 2026 *Nature* paper published on March 18th, titled "Thymic health consequences in adults", scientists used deep learning to score CT scans of over 27,000 people.[I] Higher thymic health was associated with lower all-cause mortality, lower lung cancer incidence, and lower cardiovascular mortality. It was also associated with less smoking, lower body fat, greater physical activity, better metabolic health, and lower chronic inflammation.

This makes sense. If someone looks after their health, their thymus is likely to age slower. It also indicates something else: if the thymus is aging slowly, the rest of the body probably is too.

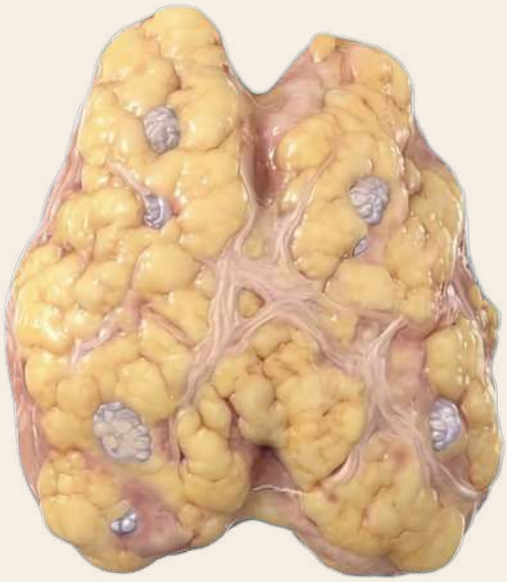
The paper suggests that how well the thymus holds up in adulthood may tell us a great deal about who stays resilient and who becomes vulnerable. Among presumably healthy participants in the screening trial, high thymic health was linked to roughly a 50% lower risk of death, a 36% lower risk of lung cancer, and nearly a 50% lower risk of dying from lung cancer compared with low thymic health.
This was an observational study, so it does not prove that fixing the thymus will directly extend life. And maybe it's just that the thymus is a canary in the coalmine. Either way, it does do something important by putting the immune system, a neglected one, back in the center of the longevity conversation.

"For decades, the thymus, a small organ tucked behind the breastbone, has been all but forgotten."

A comparison between Juvenile and Adult Thymus



Juvenile Thymus
Pre-puberty, Active Lymphoid Tissue



Adult Thymus
Involution, Adipose Replacement

IMAGE SOURCE: MEDICAL COMPARISONS VIA ADOBE STOCK, AI-GENERATED

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OPINION

HEALTHSPAN AS A FAMILY VALUE

GUEST CONTRIBUTOR:
CAROLYN B. RINGEL, JD, MBE

IMAGE SOURCE: LIV BRUCE VIA UNSPLASH

"...Extending lifespan and healthspan is a moral good, because relationships are strengthened by a healthier, longer lived older generation."

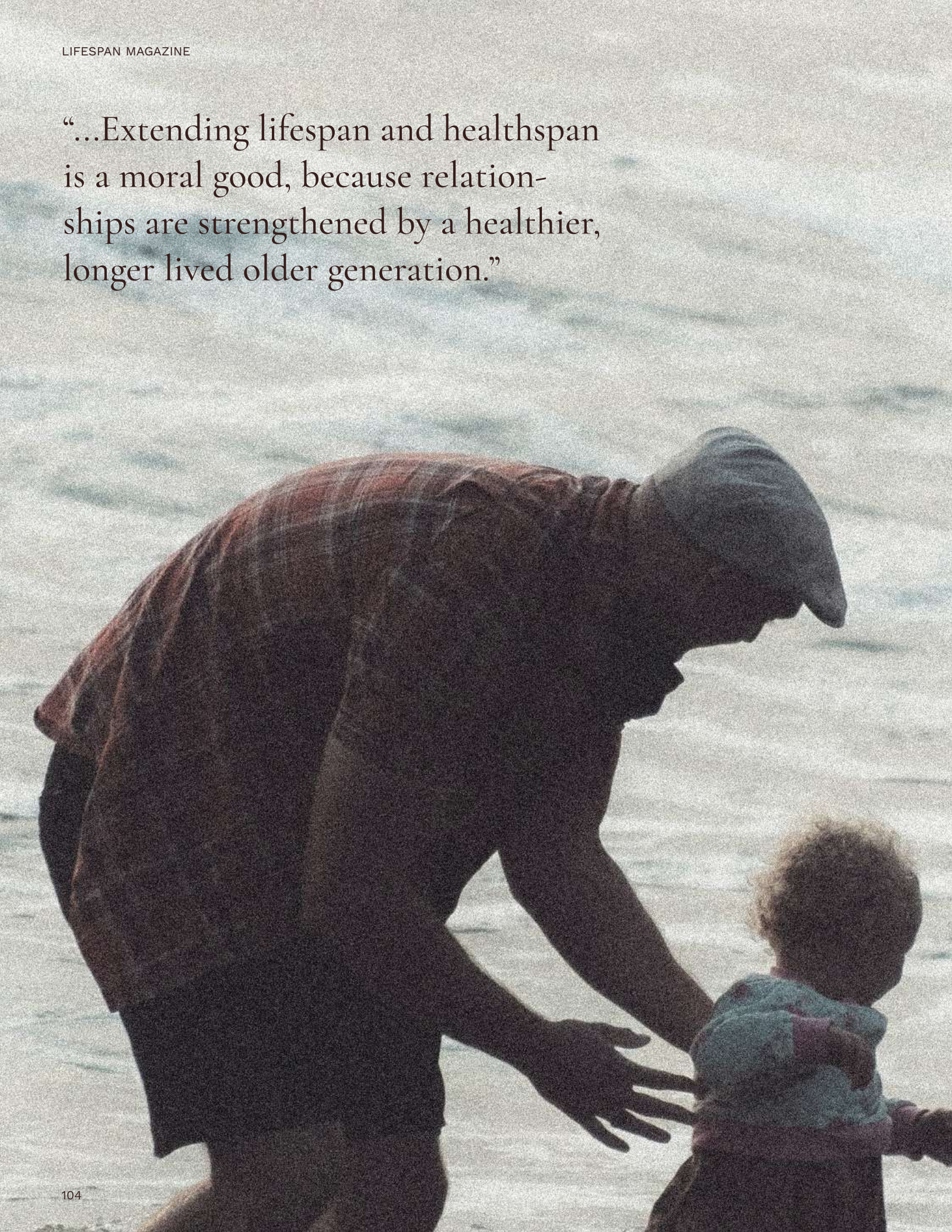

IMAGE SOURCE: GUILLAUME DE GERMAIN VIA UNSPLASH

On September 6, 2025, the Wall Street Journal published an article with the sensational headline, "The Billionaires Fueling the Quest for Longer Life."[1] The article was accompanied by a picture of four men. The media coverage of investment in aging research often reinforces the narrative that wealthy men want to invest in such research in order to extend their own lives. The subtext of this narrative is that this investment is a kind of testosterone driven ego-stroke, taking money away from worthy causes such as cancer or Alzheimer's research in order to pursue individual gain.

Moreover, when there is coverage of the many women researching healthspan and longevity, the headlines tend to focus on menopause, as if that's the only health issue on which women researchers work, or that women have to contend with as they age.

What subtly underpins both of these types of media coverage is a conception of ethics rooted in individual rights, benefits, and costs. Support for these rights may be grounded in principlism, an influential theory in bioethical discourse. Principlism argues, in part, that all individuals have a right to autonomy - that is, to make decisions around what is best for themselves and their bodies. Whether we're discussing billionaire investment or addressing menopause, the ethical argument around moving ahead with this research contends that the right to autonomy means we are entitled to promote our own health and the extension of our own lives.

But what if we apply a more feminist lens to the conversation? The ethicist and psychologist Dr. Carol Gilligan is best known for articulating a novel ethical theory called the ethics of care.[2] This theory espouses looking at not just the rights of an individual to a particular intervention, but also at how that intervention might impact broader relationships. Therefore, when evaluating the effects of longevity research, whether we are evaluating the morality of such research or where we might want to focus the research, the question we ask ourselves when applying the ethics of care is, how does such research affect not just the individual, but the individual in relation to their place in a family or in other relationships.

Perhaps the greatest strain many women (and men) are facing today is being part of what is called the sandwich generation - that is, simultaneously raising children while taking care of aging parents. But what if those elderly parents lived healthier for longer? Imagine the pressure that is lifted from middle-aged caretakers if elderly parents can participate in the family as parallel carers instead of as aging people needing care. Instead of one or two family members caring for multiple younger and older family members, you might have parents and grandparents together raising the youngest generation. In this context, under an ethics of care lens, extending lifespan and healthspan is a moral good, because relationships are strengthened by a healthier, longer lived older generation.

If we fast forward to later in a woman's life, statistically, men on average die earlier than women, leaving their spouses or partners alone.[3] It is estimated that household income drops significantly when a spouse dies, leaving many elderly women in a financially precarious position.[4] Research that seeks to address this gender gap by extending healthspan so that both partners live longer and healthier has the potential to improve the lives of both men and women at a vulnerable time at the end of their lives.

When we filter the aim of healthspan and lifespan research through the lens of the ethics of care, we find that this research is typically a moral good, because it strengthens relationships. That strength may come from relieving some of the pressure felt by women trying to juggle the roles of professional

and caregiver, or by extending the time one lives as part of a couple or family. Ultimately, the ethics of care shows us that healthspan and lifespan are indeed family values.

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The Mosaic Body

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A Bike Ride a Day Keeps the Grim Reaper Away

Does Rapamycin Block the Benefits of Exercise?

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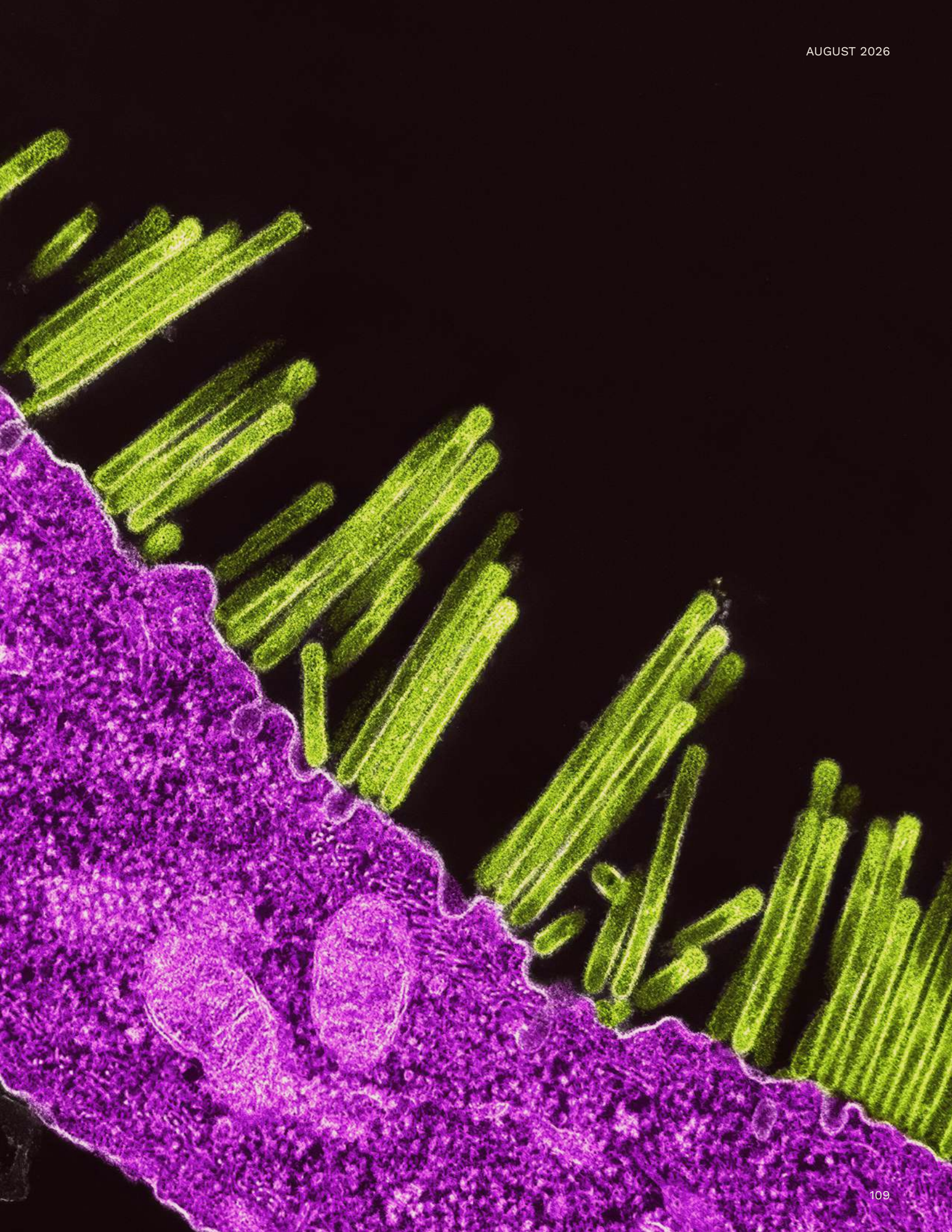
From Bedside to Cloud: David Rhew on Using AI to Help Us Age Well

IMAGE SOURCE: NATIONAL CANCER INSTITUTE, 2024 VIA UNSPLASH



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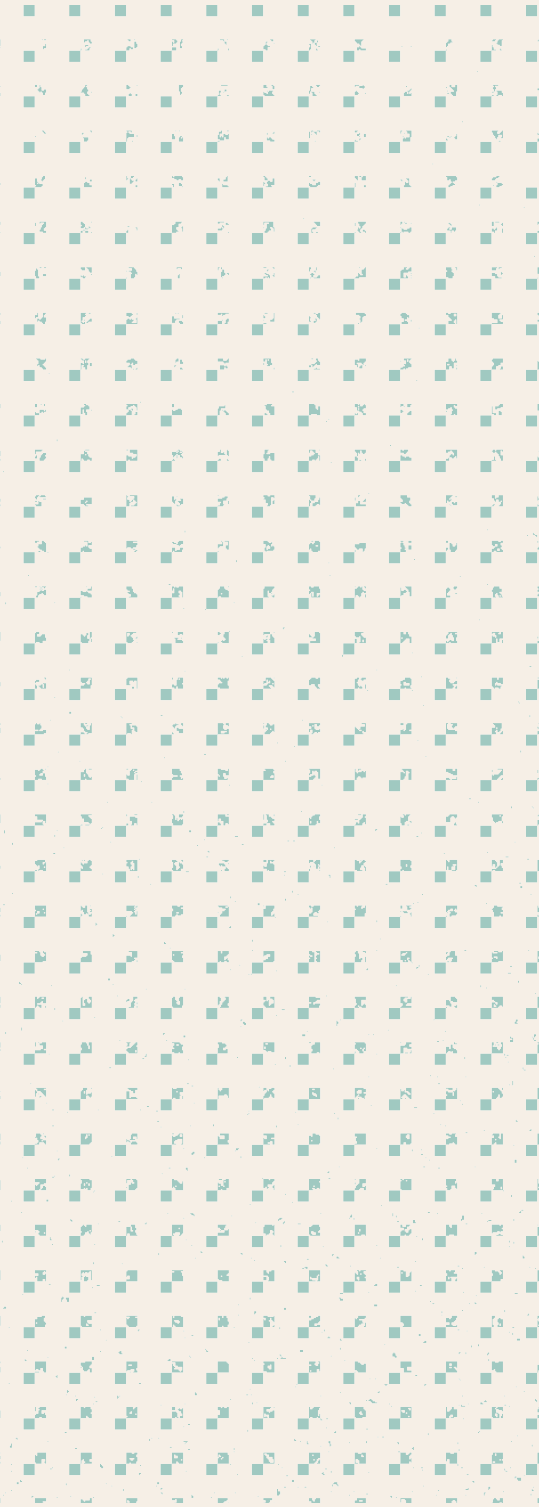

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