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SILICON VALLEY'S QUEST TO LIVE FOREVER

Can billions of dollars' worth of high-tech research succeed in making death optional?

By Tad Friend

On a velvety March evening in Mandeville Canyon, high above the rest of Los Angeles, Norman Lear's living room was jammed with powerful people eager to learn the secrets of longevity. When the symposium's first speaker asked how many people there wanted to live to two hundred, if they could remain healthy, almost every hand went up. Understandably, then, the Moroccan phyllo chicken puffs weren't going fast. The venture capitalists were keeping slim to maintain their imposing vitality, the scientists were keeping slim because they'd read—and in some cases done—the research on caloric restriction, and the Hollywood stars were keeping slim because of course.

When Liz Blackburn, who won a Nobel Prize for her work in genetics, took questions, Goldie Hawn, regal on a comfy sofa, purred, "I have a question about the mitochondria. I've been told about a molecule called glutathione that helps the health of the cell?" Glutathione is a powerful antioxidant that protects cells and their mitochondria, which provide energy; some in Hollywood call it "the God molecule." But taken in excess it can muffle a number of bodily repair mechanisms, leading to liver and kidney problems or even the rapid and potentially fatal sloughing of your skin. Blackburn gently suggested that a varied, healthy diet was best, and that no single molecule was the answer to the puzzle of aging.

Yet the premise of the evening was that answers, and maybe even an encompassing solution, were just around the corner. The party was the kickoff event for the National Academy of Medicine's Grand Challenge in Healthy Longevity, which will award at least twenty-five million dollars for breakthroughs in the field. Victor Dzau, the academy's president, stood to acknowledge several of the scientists in the room. He praised their work with enzymes that help regulate aging; with teasing out genes that control life span in various dog breeds; and with a technique by which an old mouse is surgically connected to a young mouse, shares its blood, and within weeks becomes younger.

Joon Yun, a doctor who runs a health-care hedge fund, announced that he and his wife had given the first two million dollars toward funding the challenge. "I have the idea that aging is plastic, that it's encoded," he said. "If something is encoded, you can crack the code." To growing applause, he went on, "If you can crack the code, you can *hack* the code!" It's a big ask: more than a hundred and fifty thousand people die every day, the majority of aging-related diseases. Yet Yun believes, he told me, that if we hack the code correctly, "thermodynamically, there should be no reason we can't defer entropy indefinitely. We can end aging forever."

Nicole Shanahan, the founder of a patent-management business, announced that her company would oversee longevity-related patents that Yun had pledged to the cause. "I'm here with my darling, Sergey," she said, referring to her boyfriend, Sergey Brin, the co-founder of Google. "And he called me yesterday and said, 'I'm reading this book, "Homo Deus," and it says on page twenty-eight that I'm going to die.' I said, 'It says you, personally?' He said, 'Yes!' " (In the book, the author, Yuval Noah Harari, discusses Google's anti-aging research, and writes that the company "probably won't solve death in time to make Google co-founders Larry Page and Sergey Brin immortal.") Brin, sitting a few feet away, gave the crowd a briskly ambiguous nod: *Yes, I was singled out for death; no, I'm not actually planning to die.*

After Moby put in a plug for being vegan, Dzau called on Martine Rothblatt, the founder of a biotech firm called United Therapeutics, which intends to grow new organs from people's DNA. "Clearly, it is possible, through technology, to make death optional," Rothblatt said. (She has already commissioned a backup version of her wife, Bina—a "mindclone" robot named Bina48.) Aging has long lacked the kind of vocal constituency that raised awareness of H.I.V. and breast cancer; as a species, we stink at mobilizing against a deferred collective calamity (see: climate change). The old wax fatalistic, and the young don't really believe they'll grow old. But Rothblatt suggested that the evening marked an inflection point. Turning to Dzau, she declared, "It's *enormously* gratifying to have the epitome of the establishment, the head of the National Academy of Medicine, say, 'We, too, choose to make death optional!' " The gathering blazed with the conviction that such events can spark: the belief that those inside the room can determine the fate of all those outside the room.

In the back, Andy Conrad picked up a mike to challenge the emphasis on extending maximum life span, which is currently around a hundred and fifteen. Conrad is the C.E.O. of Verily, a life-sciences firm owned by Google's parent company, Alphabet.

Like most of the scientists in the room, he aims simply to help people enjoy a few more "quality-adjusted life years." He asked, "Isn't longevity a misnomer? Isn't it 'living longer well'? Or 'healthspan'?" The biologists nodded with relief.

Norman Lear, still vigorous at ninety-four, closed the night by saying, "Seven years ago, I wrote a pilot script for a TV show called 'Guess Who Died?,' about people at a retirement community. I just learned *today* that it's on its way to being made." The audience demographics were catching up to him: by 2020, for the first time, there will be more people on Earth over the age of sixty-five than under the age of five. Lear continued, "So what I wish to offer you is, we have a stage now to get some of the things you've said tonight out to a national audience." More applause: the message would spread!

But which message? Death is optional? Or death will just have to wait?

For decades, the solution to aging has seemed merely decades away. In the early nineties, research on *C. elegans*, a tiny nematode worm that resembles a fleck of lint, showed that a single gene mutation extended its life, and that another mutation blocked that extension. The idea that age could be manipulated by twiddling a few control knobs ignited a research boom, and soon various clinical indignities had increased the worm's life span by a factor of ten and those of lab mice by a factor of two. The scientific consensus transformed. Age went from being a final stage (a *Time* cover from 1958: "Growing Old Usefully") and a social issue (*Time*, 1970: "Growing Old in America: The Unwanted Generation") to something avoidable (1996: "Forever Young") or at least vastly deferrable (2015: "This Baby Could Live to Be 142 Years Old"). Death would no longer be a metaphysical problem, merely a technical one.

The celebration was premature. Gordon Lithgow, a leading *C. elegans* researcher, told me, "At the beginning, we thought it would be simple—a clock!—but we've now found about five hundred and fifty genes in the worm that modulate life span. And I suspect that half of the twenty thousand genes in the worm's genome are somehow involved." That's for a worm with only nine hundred and fifty-nine cells. The code book is far more complex for animals that excite our envy: the bee larva fed copiously on royal jelly that changes into an ageless queen; the Greenland shark that lives five hundred years and doesn't get cancer; even the humble quahog clam, the kind used for chowder, which holds the record at five hundred and seven.

For us, aging is the creeping and then catastrophic dysfunction of everything, all at once. Our mitochondria sputter, our endocrine system sags, our DNA snaps. Our sight and hearing and strength diminish, our arteries clog, our brains fog, and we falter, seize, and fail. Every research breakthrough, every announcement of a master key that we can turn to reverse all that, has been followed by setbacks and confusion. A few years ago, there was great excitement about telomeres, Liz Blackburn's specialty—DNA buffers that protect the ends of chromosomes just as plastic tips protect the ends of shoelaces. As we age, our telomeres become shorter, and, when these shields go, cells stop dividing. (As Blackburn said, "It puts cells into a terribly alarmed state!") If we could extend the telomeres, the thinking went, we might reverse aging. But it turns out that animals with long telomeres, such as lab mice, don't necessarily have long lives—and that telomerase, the enzyme that promotes

telomere growth, is also activated in the vast majority of cancer cells. The more we know about the body, the more we realize how little we know.

Still, researchers plunge ahead. Understanding isn't a precondition for successful intervention, they point out; we had no real grasp of virology or immunology when we began vaccinating people against smallpox.

In the murk of scientific inquiry, every researcher looks to a ruling metaphor for guidance. Aubrey de Grey likes to compare the body to a car: a mechanic can fix an engine without necessarily understanding the physics of combustion, and assiduously restored antique cars run just fine. De Grey is the chief science officer of Silicon Valley's SENS Research Foundation, which stands for Strategies for Engineered Negligible Senescence—a fancy way of saying "Planning Your Comprehensive Tune-up." An Englishman who began his career with a decade of work in A.I., he speaks with rapid fluidity, often while stroking his Rasputin-length beard. De Grey has proposed that if we fix seven types of physical damage we will be on the path to living for more than a thousand years (assuming we can avoid getting hit by a bus or an asteroid).

When I met him at the SENS office, in Mountain View, he told me, "Gerontologists have been led massively astray by looking for a root cause to aging, when it's actually that everything falls apart at the same time, because all our systems are interrelated. So we have to divide and conquer." We just need to restore tissue suppleness, replace cells that have stopped dividing and remove those that have grown toxic, avert the consequences of DNA mutations, and mop up the gunky by-products of all of the above. If we can disarm these killers, de Grey suggests, we should gain thirty years of healthy life, and during that period we'll make enough further advances that we'll begin growing biologically younger. We'll achieve "longevity escape velocity."

De Grey vexes many in the life-extension community, and one reason may be his intemperate life style. He told me, "I can drink as much as I like and it has no effect. I don't even need to exercise, I'm so well optimized." Until recently, he maintained two girlfriends and a wife. Now, he said, "I'm engaged, and my polyamorous days are behind me."

But the main reason is his prophetic air of certainty. His 2007 book, "Ending Aging," is replete with both exacting research into the obstacles to living longer and proposed solutions so ambitious that they resemble science fiction. De Grey's fix for

mitochondrial mutation, for instance, is to smuggle backup copies of DNA from the mitochondria into the vault of the nucleus, which evolution annoyingly failed to do—probably because the proteins needed in the mitochondria would ball up during their journey through the watery cell body. His fix for that, moving the DNA one way and the proteins that it produces another, amounts to a kind of subcellular hokey pokey. A number of scientists praise de Grey for anatomizing the primary threats, yet they see troubleshooting all seven pathways through such schemes—and you have to troubleshoot them all for his plan to work—as a foredoomed labor. Matt Kaeberlein, a biogerontologist at the University of Washington, said, "It's like saying, 'All we have to do to travel to another solar system is these seven things: first, accelerate your rocket to three-quarters of the speed of light . . .' "

The great majority of longevity scientists are healthspanners, not immortalists. They want to give us a healthier life followed by "compressed morbidity"—a quick and painless death. These scientists focus on the time line: since 1900, the human life span has increased by thirty years—and so, as a consequence, have cancer, heart disease, stroke, diabetes, and dementia. Aging is the leading precondition for so many diseases that "aging" and "disease" are essentially metonyms. Accidents and violence are the leading causes of death up to age forty-four, then cancer rises to the top, and then, at sixty-five, heart disease. Healthspanners want to understand the etiologies of cancer and heart disease and then block them. Why do we almost never get those diseases at age two? How can we extend that protection to a hundred and two? But if we cured cancer we would add only 3.3 years to an average life; solving heart disease gets us an extra four. If we eliminated all disease, the average life span might extend into the nineties. To live longer, we'd have to slow aging itself.

Even if we do that, the healthspanners believe, we're not going to live forever—nor should we. They worry about the rapid drain on natural resources and on Social Security; the potential for a Stalin or a Mugabe to stay in power for centuries; the loss of new ideas from the young; and profound lifelong boredom. Amy Wagers, a researcher at Harvard, told me, "Part of the meaning of life is that we die." The Greeks warned about the danger of grasping for godlike powers. It didn't work out well for Asclepius or Achilles, and it worked out even worse for Tithonus, whose lover, Eos, begged Zeus to grant him eternal life but forgot to request eternal youth as well. Decrepit, senile, and miserable, Tithonus eventually shrank into a cicada who stridulated ceaselessly, calling out for release.

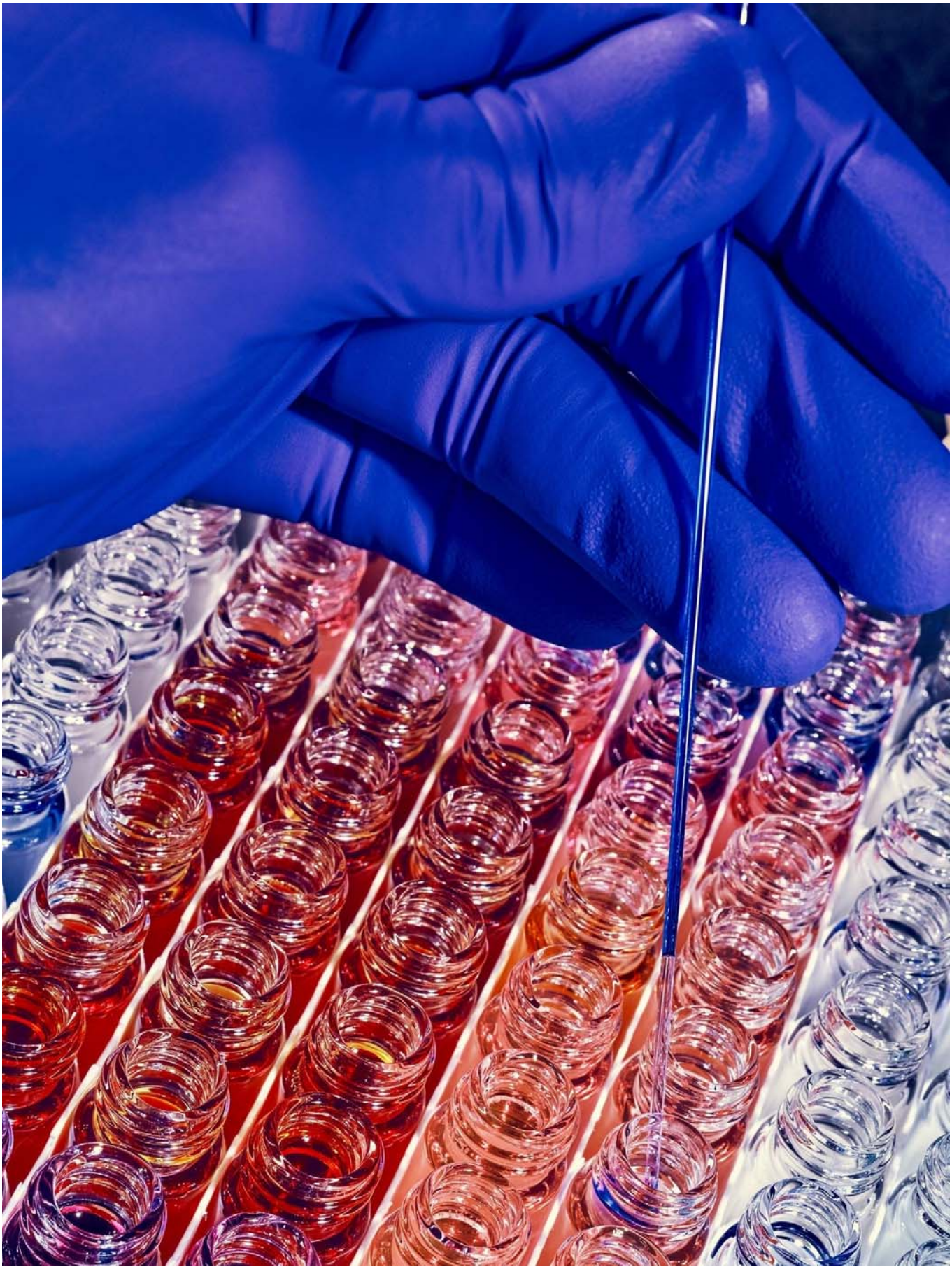
When I met Ned David, I thought that he was about thirty. He had an unlined face and thick auburn hair, he walked rapidly with his hands stuffed into his jeans pockets, and he wore red Converse high-tops.

David is forty-nine. He is a biochemist and a co-founder of a Silicon Valley startup called Unity Biotechnology. Unity targets senescent cells—cells that, as they age, start producing a colorless, odorless, noxious goo called SASP, which Unity's researchers call "the zombie toxin," because it makes other cells senescent and spreads chronic inflammation throughout the body. In mice, Unity's treatments delay cancer, prevent cardiac hypertrophy, and increase median life span by thirty-five per cent. "We think our drugs vaporize a third of human diseases in the developed world," David told me.

David isn't taking any of Unity's drugs, which won't be on the market for at least seven years. His youthfulness derives from existing therapies: he takes metformin—a diabetes drug that has made elderly diabetics live *longer* than a healthy control group—and Retin-A, for his skin. He also swims a lot, having quit running because of spinal osteoarthritis. "I am often accused, here, of picking the things we work on based on the problems of aging I have," David said. "But because of our drugs I predict that I will run again!"

A systemic approach to aging, which would ideally result in your general practitioner prescribing you a "God pill," is philosophically attractive but financially infeasible. Pharma and biotech companies make money only if they treat a disease, and, because aging affects everything, the F.D.A. doesn't recognize it as an "indication" susceptible to treatment (or to insurance-company reimbursement). So Unity is taking aim at glaucoma, macular degeneration, and arthritis; the fridge in its lab is stocked with human eyeballs and knee cartilage. This is the customary serial-specialist approach to aging, which tackles it symptom by symptom: let's restore those eyes, then send you down the street for a 3-D-printed kidney.

Last fall, Unity raised a hundred and sixteen million dollars from such investors as Jeff Bezos and Peter Thiel, billionaires eager to stretch our lives, or at least their own, to a span that Thiel has pinpointed as "forever." In a field rife with charlatans, Ned David's Dorian Gray affect has factored into his fund-raising. "One class of investor, like Fidelity, finds my youthful appearance alarming," he said. "Another class—the Silicon Valley type, a Peter Thiel—finds anyone who looks over forty alarming."



In mice, Unity Biotechnology's treatments delay cancer, prevent cardiac hypertrophy, and increase median life span by thirty-five per cent. "We think our drugs vaporize a third of human diseases in the developed world," one executive said. Photograph by Grant Cornett for The New Yorker

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Traditionally, it has been the graying tycoons of technology who funded aging research, hoping to disrupt the three-act structure of the Silicon Valley journey: life hacker, rock climber, cadaver. Now aging has cachet in the startup world. Arram Sabeti, the thirty-year-old founder of a tech company called ZeroCater, told me, "The proposition that we can live forever is obvious. It doesn't violate the laws of physics, so we will achieve it." Sabeti spends his leisure time reading all-cause-mortality metastudies, and is an investor in the Longevity Fund, a venture fund recently launched by Laura Deming. Deming, who is twenty-two, terms the longevity market a "two-hundred-billion-dollar-plus" opportunity, but she told me that "it's really impossible to say how big it could be, because if you cured aging you'd change medicine entirely."

Unsurprisingly, it was Google that transformed the Valley's view of aging. Surprisingly, perhaps, it was the company's Bill Maris who was in the vanguard. As the founder and C.E.O. of Google Ventures, Maris led successful investments in companies such as Nest and Uber; he was amiable, admired, and financially secure—not an obvious modern-day alchemist. However, he told me, "My thoughts can turn to dark things when I'm alone." His father died of a brain tumor in 2001, when Maris was twenty-six. "I majored in neuroscience, I've worked in hospitals, but until my father died I did not understand the finality of 'Gone, never to be seen again,' " he said.

Maris, who is forty-two, is a longtime vegetarian who works out on an elliptical machine for an hour every day. He comforts himself with the knowledge that the scientist who performed a 3-D scan of his brain praised his robust corpus callosum, the bundle of nerve fibers that connects the hemispheres. (Maris displays gleaming polymer models of his and his wife's brains under glass bells in his office.) But such precautions and advantages were temporary, personal stopgaps. How could he fix the problem permanently, and for everyone?

He decided to build a company that would solve death. He discussed the idea with Ray Kurzweil, the futurist who popularized the concept of the Singularity—the idea that humans will merge with A.I. and transcend our biological limitations—and Kurzweil was enthusiastic. Maris also discussed it with Andy Conrad, the geneticist who runs Alphabet's Verily, and Conrad was thoughtfully discouraging. The first problem was the long study time in humans: it's hard to run a clinical trial on subjects who take eighty years to die. (A related issue is that we have no accepted

model for how to measure biological age, which often differs significantly from chronological age. Seventy probably isn't the new fifty for, say, Ozzy Osbourne.) The second problem was the immense difficulty of determining whether any seeming cause of aging was actually causal, or merely a correlative of some other, stealthier process.

"Andy did throw a lot of cold water on the idea," Maris said. "But there were no issues of fact. He didn't say, 'Aging isn't a genetic disease,' or 'Google will never fund this.' " In 2011, Maris pitched his proposed company to John Doerr, a prominent venture capitalist who is on Alphabet's board. "Imagine you found a lamp on the beach, and a genie came out and granted you a wish," Maris said. "If you were clever, your first wish would be for unlimited wishes." As Doerr nodded, Maris continued, "Let's say you're going to live, at most, another thirty years." Doerr had just turned sixty. "If each day is a wish, that's only between one and ten thousand wishes. I don't know about you, but I want to add more—I want to add wishes faster than they're taken away." Doerr, confronted with the limits to his life span, was galvanized. When Maris pitched Google's founders, Sergey Brin, who has a gene variant that predisposes him to Parkinson's disease, loved the idea, and Larry Page declared, "We should do it here!"

In 2013, Google launched Calico, short for the California Life Company, with a billion dollars in funding. "Calico added a tremendous amount of validation to aging research," George Vlasuk, the head of a biotech startup called Navitor, told me. "They have money, brainpower, and time." But Calico has proved to be extremely secretive. All that's known is that it's tracking a thousand mice from birth to death to try to determine "biomarkers" of aging—biochemical substances whose levels predict morbidity; that it has a colony of naked mole rats, which live for thirty years and are amazingly ugly; and that it has invested in drugs that may prove helpful with diabetes and Alzheimer's. (The company declined to comment.)

A number of longevity scientists confess to disappointment with Calico's direction. Nir Barzilai, a geneticist who is a leader in the aging field, told me, "The truth is, we don't know *what* they're doing, but whatever it is doesn't really seem to be attacking the problem." Another scientist who's familiar with Calico's workings said that it's pursuing its mission judiciously, but that the company began, fatally, as a vanity project. The scientist said, "This is as self-serving as the Medici building a Renaissance chapel in Italy, but with a little extra Silicon Valley narcissism thrown

in. It's based on the frustration of many successful rich people that life is too short: 'We have all this money, but we only get to live a normal life span.' "

Maris, who has retired from Google Ventures, strongly disagreed with that view. "This is not about Silicon Valley billionaires living forever off the blood of young people," he said. "It's about a 'Star Trek' future where no one dies of preventable diseases, where life is fair."

If Silicon Valley billionaires end up being sustained by young blood, they will satisfy an ancient yearning. In 1615, a German doctor suggested that "the hot and spirituous blood of a young man will pour into the old one as if it were from a fountain of youth." In 1924, the physician and Bolshevik Alexander Bogdanov began young-blood transfusions, and a fellow-revolutionary wrote that he "seems to have become seven, no, ten years younger." Then Bogdanov injected himself with blood from a student who had both malaria and tuberculosis, and died. Parabiosis, the surgical linkage of circulatory systems, has had a mostly grisly history in humans —when it was tried as a desperate measure on terminal cancer patients, in 1951, a two-year-old boy lost part of his foot to gangrene—and in rodents, which resisted being conjoined. A 1956 study warned, "If two rats are not adjusted to each other, one will chew the head of the other until it is destroyed."

We kept trying. In 2005, a Stanford lab, run by a stem-cell biologist and neurologist named Tom Rando, announced that heterochronic parabiosis, or an exchange of blood between older and younger mice, rejuvenated the livers and muscles of the older ones. Vampires everywhere felt validated. Last fall, on "The Late Show," Stephen Colbert warned teen-agers that President Trump would replace Obamacare with mandatory parabiosis: "He's going to stick a straw in you like a Capri Sun."

Entrepreneurs and venture capitalists also had their straws poised. Rando said, "I've had a lot of meetings with young billionaires in Silicon Valley, and they all, to varying degrees, want to know when the secrets are coming out, both so they can get in on the next big thing and so they can personally take advantage of them. I say, 'This is not an app. If you come at biology from a tech point of view, you're going to be disappointed, because the pace is much slower.' "

In recent years, the parabiosis field has grown quarrelsome. Is the rejuvenative key the presence of young-blood proteins, or the absence of something like SASP? Could it be a cellular by-product from one mouse, or the effect of borrowing a younger

mouse's liver? In 2014, the Harvard scientist Amy Wagers concluded that young-blood factors, particularly a protein called GDF11, gave older mice a stronger grip and renewed their brains. Most of her colleagues questioned her results, and the drug company Novartis promptly did a study that suggested the exact opposite: you should *blockade* GDF11. Wagers told me, "Different groups have reported that amounts of GDF11 go up, go down, or stay the same with age." With a bleak laugh, she added, "Clearly, one group is right."

After Rando's colleague Tony Wyss-Coray showed that young blood can foster new neurons in the hippocampus region of the brains of old mice, a company called Alkahest spun out from his work. Alkahest has begun to sift the more than ten thousand proteins in plasma, in hopes that the right protein cocktail can cure Alzheimer's—a process that is expected to continue for more than a quarter century.

When I visited Alkahest recently, Joe McCracken, the vice-president of business development, cued up side-by-side videos of genetically identical, equally aged mice. They were about to run a Barnes maze: a disk dotted with black circles, one of which was a hole—a laboratory version of a burrow in which to escape a diving hawk. During previous runs, they'd been trained to remember the hole's location. McCracken, who was with two colleagues, explained that the first mouse had been treated only with a placebo of inert saline. We watched it nose here and there, uncertainly, before finally stumbling upon the hole. It took a minute and twenty seconds. The men clapped, releasing their anxiety. "It's me in the parking lot, looking for my car," Sam Jackson, the company's chief medical officer, said. Then McCracken played the video of a mouse that had been tuned up with plasma from eighteen-year-old human beings. That mouse darted purposefully toward one sector of the maze, found the hole, and scooted into it in eighteen seconds. The execs grinned and shook their heads: youth.

Every longevity experimenter has talismanic photos or videos of two mice: one timid and shuffling, with patchy fur; the other sleek and vital, thrumming with the miracle elixir. But can mice be our proxy? Empathy beguiles us into believing so. When you read that mice made to run on a treadmill were given "a five-minute warmup period and a five-minute cooldown period," you think, Very sensible. Yet mice don't have heart attacks, and their muscles start wasting suddenly, rather than gradually, as ours do. Mice also don't get Alzheimer's disease, so scientists mimic it by breeding mice with genes taken from humans. But, since we get Alzheimer's only when we're old, testing treatments in young mice often proves misleading. It doesn't

help that labs use radiation to cause artificial aging, or that lab mice live much longer than wild mice. Tony Wyss-Coray told me, "People say, 'The young mouse finds the hole—O.K., we're good, give me the treatment!' And I say, 'We don't know if it's safe, we don't know if mice are the same as humans—you have to wait.' " We've cured cancer in lab mice dozens of times, and made them live twice as long, yet none of those results have transferred upstream. "So many times, the mice have failed us," the geneticist Nir Barzilai lamented.

The reigning view among longevity scientists is that aging is a product not of evolutionary intent but of evolutionary neglect: we are designed to live long enough to pass on our genes, and what happens afterward doesn't much matter. As the geroscientist Richard A. Miller wrote, "Mice that devote their energies to eating and breeding will do better than those that spend valuable capital on eye repair and anticancer surveillance." We mature more slowly than mice and live much longer, because we, like whales and naked mole rats, are at much less risk of being eaten in our first year. Yet from the age of thirty or forty on, after we've spawned, we're living on time that evolution regards as pointless. Eric Verdin, the C.E.O. of the Buck Institute for Research on Aging, the leading nonprofit in the field, noted that "if you just kept aging at the rate you age between twenty and thirty, you'd live to a thousand. At thirty, everything starts to change." From that point, our risk of mortality doubles every seven years. We're like salmon, only we die in slow motion.

The battle between healthspanners and immortalists is essentially a contest between the power of evolution as ordained by nature and the potential power of evolution as directed by man. The healthspanners see us as subject to linear progress: animal studies take the time that they take; life sciences move at the speed of life. Noting that median life expectancy has been increasing in developed nations by about two and a half years a decade, Verdin told me, "If we can keep that pace up for the next two hundred years, and increase our life spans by forty years, that would be *incredible*."

The immortalists have a different view of both our history and our potential. They see centuries of wild theorizing (that aging could be reversed by heating the body, or by breathing the same air as young virgins) swiftly replaced by computer-designed drugs and gene therapies. Bill Maris said, "Health technology, which for five thousand years was symptomatic and episodic—'Here are some leeches!'—is becoming an information technology, where we can read and edit our own genomes."

Many immortalists view aging not as a biological process but as a physical one: entropy demolishing a machine. And, if it's a machine, couldn't it be like a computer? Progress in computers, or anyway in semiconductors, has been subject to Moore's Law, the exponential flywheel that has doubled capacity every two years. In linear progress, after thirty iterations you've advanced thirty steps; in exponential progress, you've advanced 1.07 billion steps. Our progress in mapping the human genome looked like it was linear—and then was revealed, once the doublings grew significant, as exponential.

A number of startups are trying to harness exponential curves. BioAge has been using machine learning and crunching genomics data to search for biomarkers that predict mortality. Kristen Fortney, the company's thirty-four-year-old C.E.O., told me that she had also begun testing computationally designed drugs to find an unexpected substance that would powerfully affect those markers. She's about to seek her next round of venture financing, and she's optimistic: "Biotech is something a lot of V.C.s don't understand, but machine learning and big data are things they do understand."

Aging doesn't seem to be a program so much as a set of rules about how we fail. Yet the conviction that it must be a program is hard to dislodge from Silicon Valley's algorithmic minds. If it is, then reversing aging would be a mere matter of locating and troubleshooting a recursive loop of code. After all, researchers at Columbia University announced in March that they'd stored an entire computer operating system (as well as a fifty-dollar Amazon gift card) on a strand of DNA. If DNA is just a big Dropbox for all the back-office paperwork that sustains life, how hard can it be to bug-fix?

In July, Brian Hanley, a sixty-year-old microbiologist who lives in Davis, California, began trying to give himself the equivalent of an operating-system update: he injected analogues of the gene for growth-hormone-releasing hormone, or GHRH, into his left thigh. GHRH is normally produced in the brain, but Hanley was essentially turning a pencil-eraser-size part of his thigh into a gland that made the molecule, which stimulates the heart, the kidneys, and the thymus. He believed that the treatment was working. His testosterone and good cholesterol were up, his heart rate and bad cholesterol were down, his eyesight was keener. And there was a peculiar side effect: euphoria. On one bike ride, when his bike began to topple sideways, he just let it take him down, laughing.

When I met with him, though, he moved gingerly around his dining-room table, unable to sit for long. A few days earlier, he'd herniated a disk trying to lift a refrigerator. It was his fourth significant injury since beginning his gene therapy, but he assured me that this was a common problem for people taking a course of regenerative medicine: they feel so good that they try to do too much. When George Church, a Harvard geneticist whose lab collaborates with Hanley, heard about his injuries, he told me, "It sounds like it affected his mind more than his muscles."

For those frustrated by the stately progress of research up the animal chain, from worms to flies to mice to dogs to monkeys, speculative treatments abound. In Monterey, California, a clinic will give you young plasma for eight thousand dollars a pop—but you have no idea what it's doing to you. Peter Nygård, a leonine seventy-five-year-old Finnish-Canadian clothing designer who got rich making women look slim in modestly priced pants, has had injections with stem cells derived from his DNA. He believes that the process has reversed his aging. In an interview a few years ago, he proclaimed, "I'm the only guy in the world today who has me, in a petri dish, before I was born."

Researchers store vials of aging cells in liquid nitrogen for use in future experiments. If work progresses slowly, some also plan to freeze themselves, with instructions to reawaken them once science has finished paving the way to immortality. Photograph by Grant Cornett for The New Yorker

Photograph by Grant Cornett for The New Yorker

While Hanley has a tinkerer's mentality—there's a hyperbaric chamber stuffed behind his couch—he's a dedicated researcher. Since the F.D.A. requires an authorization for any new tests on humans, he began trying therapies on himself. He'd read the literature on self-experimentation, and tallied the results: eight deaths (including that of the blood-transfusing Alexander Bogdanov), and ten Nobel Prizes. Coin toss.

Hanley acknowledged that his research had a few basic problems as a template for reshaping life spans. First, a sample size of one; second, a therapeutic method whose results may not last; third, a gene whose effects seem to be regenerative rather than transformative. In order to comprehensively reprogram ourselves, we'd want to insert corrective genes into a virus that would disperse them throughout the body, but doing so could alarm the immune system.

The advent of CRISPR, a gene-editing tool, has given researchers confidence that we're on the verge of the gene-therapy era. George Church and his Harvard postdocs have culled forty-five promising gene variants, not only from "super centenarians"—humans who've lived to a hundred and ten—but also from yeast, worms, flies, and long-lived animals. Yet Church noted that even identifying longevity genes is immensely difficult: "The problem is that the bowhead whale or the capuchin monkey or the naked mole rat, species that live a lot longer than their close relatives, aren't that close, genetically, to those relatives—a distance of tens of millions of genetic base pairs." The molecular geneticist Jan Vijg said, "You can't just copy a single mechanism from the tortoise," which can live nearly two hundred years. "We'd have to turn our genome over to the tortoise—and then we'd be a tortoise."

Becoming part tortoise wouldn't necessarily alarm Brian Hanley. If we can only find the right genes and make their viral transmission safe, he declared, "we can enable human transformations that would rival Marvel Comics. Super muscularity, ultra-endurance, super radiation-resistance. You could have people living on the moons of Jupiter who'd be modified in this way, and they could physically harvest energy from the gamma rays they were exposed to."

Although Ned David has maintained his milk-fed aspect by battling his own aging on multiple fronts, down to his choice of sneakers, he can't shake the idea that our foe is fundamentally unitary. David likens longevity research to a huge tree, and he believes that most current efforts, including the therapies his company is

pursuing, are just branches of the tree. "No one is working on the trunk," he told me, mournfully. In December, however, he began to have hope that "trunkness," as he puts it, was in sight.

David had long suspected that the epigenome was central to longevity. If the genome is our cellular hardware, then the epigenome is its software: it's the code that activates DNA, telling a cell to differentiate—to become a macrophage or a neuron—and then how to remember its identity. The epigenome itself is controlled by agents that add or subtract chemical groups, known as marks, to its proteins. Biologists suspect that when the epigenome accumulates too many marks, over time, the signals it sends to cells change dramatically—and that those new signals produce the effects of aging. This process could explain, for instance, why an old person's skin can refresh itself with new cells every month and yet continue to look old.

In 2012, Tom Rando and his Stanford colleague Howard Chang published a paper noting that a fertilized human egg has properties of eternal youth: sperm and eggs can age, but every embryo resets the clock. Chang, a dermatologist and genome scientist, had discovered that the epigenome in aging skin, once it has accumulated enough marks, turns the genome on with a protein called NF-kB in ways that inflame and age skin. When he inhibited NF-kB in genetically modified mice, it rejuvenated their skin. Rando's work in parabiosis seemed to hinge on a similar process: making stem cells revert to a more youthful stage. The scientists suggested that "the ideal would be to reset the aging clock but to leave the differentiation program untouched"—that is, to engage the stem cells and make them refresh tissues and organs without making them revert to a predifferentiated state, which would introduce hairy, tooth-filled tumors called teratomas. The goal was young-Brad-Pitt-stage Benjamin Button, nothing more.

After that paper, Rando turned back to parabiosis, and Chang began work on a cream to make skin look decades younger. He explained, "That's what people want." But he also said that the longevity community had proved too fractious: "It's the most difficult field I've ever worked in, and I didn't want to define my scientific life with all these fights."

In December, Juan Carlos Izpisua Belmonte, of the Salk Institute, in San Diego, announced that he'd done the work that Rando and Chang had proposed. After four years of trial and error in mouse experiments, he had figured out a way to trigger the Yamanaka factors, four genes that reset the clock in fertilized eggs. When lab mice

drank water laced with doxycycline—but only two days a week—they lived more than thirty per cent longer. Wild mice subjected to the same method had rejuvenated muscles and pancreases.

As in most modern efforts to circumvent aging, Belmonte was tricking the body—borrowing a powerful mechanism from embryos and, very gingerly, applying it to adults. He told me, "You want a cardiac cell to become a new cardiac cell, but not to revert all the way to a stem cell, which would stop the heart beating. We did that. Our experiment was very rude and uncontrollable, and there will be other deleterious effects, as well as many unknowns. But this is very promising." Modifying cells' software was less dangerous than tampering with their hardware, he said, and, as with software, "there will always be a better version of our program next year." Belmonte was careful to downplay the obvious question that his research provoked: If we could keep resetting our clock, couldn't we live indefinitely? "The idea is not to increase life span but to have yourself working better," he told me. He chuckled, and added, "Obviously, if you improve all the cells in your body, as an indirect consequence you will live longer."

Galvanized by Belmonte's work, Ned David flew to San Diego twice this winter to meet with him and see if there was a way "to prove that this was the ticking clock" and then to "nudge us back to twenty-five-ness." In mid-March, they discussed ways to proceed. Could they develop markers so that cells would change color in the lab if a drug made them younger—and change to a different color if they were perturbed too far? Could the team activate telomerase to rejuvenate the epigenome? Could they find genes that would act as an emergency brake on the reversion process? There was so much systems logic to think through.

David was tantalized by the possibility of trunkness, yet still unsure. "We can revert some tissues, in a shotgunny way," he said, "but we haven't figured out the Francis Crick experiment that changes everything." He laughed. "If I knew what *that* experiment was, I'd be doing it now." Even if Belmonte and David find a substance that rejuvenates stem cells the perfect, Goldilocks amount, there will likely be unexpected side effects—for the hip bone is connected not only to the thigh bone but to every other damn bone. To repair tissue, you need to rejuvenate stem cells. But stem cells need to divide to do their job, and the division process invites random mutations—which drive cancer.

A great many longevity papers end with mystified hand-waving in the direction of unknown "systemic factors." Solving aging is not just a whodunnit but a howdunnit and wheredunnit and a whyohwhydunnit. Tom Rando suggested, "It's not A causes B causes C causes D causes aging. It's a network diagram of nodes and links—all subject to feedback loops where consequences become causes—that gradually becomes more and more destabilized." If the body is a set of Christmas-tree lights—and it's not—then every time you plug it into a new outlet some lights go on and some go off. Stabilizing one part of the network further destabilizes another. That which makes us also unmakes us, and the process of living seems inextricably bound to the process of dying.

So far, the most powerful interventions you can make to extend your life are the kinds of low-tech things that your doctor has already told you in a droning voice. Quit smoking (ten more years) and wear a seat belt (two more). Assuming you've already done that, exercise regularly and watch your diet. Pankaj Kapahi, a researcher at the Buck Institute, recently showed me two clear boxes filled with fruit flies in vials, with two types of food at the bottom: orange goo in one set of vials and yellow goo in the other. "These are the flies on the burger diet, these are the flies on the Spartan diet," he said, pointing to the boxes. "You can gauge their health by how quickly they go up the vial." He banged both boxes, hard. The burger-fed flies struggled upward, while the Spartan flies soared. "Some of these diets can double their life spans," he said.

Both caloric restriction and exercise appear to dampen mTOR, a signalling pathway that regulates cellular metabolism. Under strain, the body realizes that it's a bad time to reproduce and a good time to repair cells and increase stress resistance. Scientists believe this is nature's way of responding to famine: hunker down and wait for better times to procreate. There seems to be a link between forgoing sex and extending life, since what the French call the little death apparently hastens the big one. The immune suppressant rapamycin makes mice live longer, yet shrivels their testicles. Likewise, the most proven way for a man to live fourteen years longer than average is to become a eunuch. Good news/bad news.

Starving yourself, unsurprisingly, has disadvantages. If you want caloric restriction to have a chance of working, you should take in at least thirty per cent fewer calories, and the most useful way to do that—intermittent fasting—is both unpleasant for subjects to endure and impossible for researchers to patent. So the goal is to develop powerful drugs that subdue mTOR without making you feel famished. In the

meantime, the Calorie Restriction Society's Web site warns you to be careful how you go about limiting your intake: "Sudden adult onset calorie restriction shortens the lifespans of mice." The site goes on to say, "There are several other risks you should be aware of"—at which point the page breaks off.

Leonard Guarente, an M.I.T. biology professor who did important research on the mTOR-regulating enzymes called sirtuins—which seemed like a potential master key a decade ago—is a co-founder and the chief scientist of Elysium Health. Elysium's first nutraceutical product, called Basis, promises "metabolic repair and optimization." For fifty dollars a month, a daily pill provides you with chemicals that nourish sirtuins. There are no clinical data yet that Basis does anything useful in humans, so, when I visited Guarente in his office at M.I.T., I asked if he'd noticed any effects from taking it. "I *have*," he said. He glanced at Elysium's P.R. person. "Can I say it? It is O.K.?" She gave a calibrated nod, and he said, "*My fingernails grow faster*." And what does that mean? "I don't know. But *something*."

All the leading immortalists started out in tech, and all had a father who died young (as Ray Kurzweil's did when he was twenty-two), or absconded early (as Aubrey de Grey's did before he was born). They share an early loss of innocence and a profound faith that the human mind can perfect even the human body. Larry Ellison, the co-founder of Oracle, lost his adoptive mother to cancer when he was in college—and later donated three hundred and seventy million dollars to aging research. "Death has never made any sense to me," he told a biographer. "How can a person be there and then just vanish?" Bill Maris, who conceived of Calico, said that, when he pondered the inevitability of death, "I felt it was maybe our mission here to transcend that, and to preserve consciousness indefinitely."

Immortalists fall into two camps. Those who might be called the Meat Puppets, led by de Grey, believe that we can retool our biology and remain in our bodies. The RoboCops, led by Kurzweil, believe that we'll eventually merge with mechanical bodies and/or with the cloud. Kurzweil is a lifelong fixer and optimizer: early in his career, he invented the flatbed scanner and a machine that reads books aloud to the blind. Those inventions have improved dramatically in subsequent iterations, and now he's positive that what he calls "the law of accelerating returns" for human longevity is about to kick in.

I met with Kurzweil at Google, where he is a director of engineering, but he emphasized that he was speaking in his private capacity as a futurist. Though a few

days short of his sixty-ninth birthday, he looked much younger. After discovering, in his thirties, that he had Type 2 diabetes, he changed his life style radically and began taking supplements. He swallows some ninety pills a day, including metformin; Basis; a coenzyme called Q10, for muscle strength; and phosphatidylcholine, to keep his skin supple. "How does it look?" he asked me, plucking at his forearm. "Supple!" I said.

Kurzweil thinks of such efforts, which attempt to slow aging by using current technology, as Bridge One to indefinite longevity. But he also subscribes to the belief that the body is essentially a computer made up of overwritable data and updatable apps. Therefore, we'll soon be in the midst of a biotech revolution, which will offer personally tailored immune therapies for cancer as well as organs grown from our own DNA. This is Bridge Two, which he believes will bring us to longevity escape velocity within about fifteen years. "I'm actually a little more optimistic than Aubrey," he said. Bridge Three, which he expects us to cross by the two-thousand-thirties, is nanobots—blood-cell-size devices that will roam the body and the brain, cleaning up all the damage that de Grey wants to fix with medical interventions. "I used to call it the killer app of health technology," Kurzweil said, "but that's not a good name."

When we cross Bridge Four, those same nanobots will connect our brains to a neocortical annex in the cloud, and our intelligence will quickly expand a billionfold. Once that transformation happens, in 2045, the Singularity occurs and we become like gods. "For a time, we'll be a hybrid of biological and nonbiological thinking, but, as the cloud keeps doubling, the nonbiological intelligence will predominate," Kurzweil said. "And it will be anachronistic, then, to have one body." He raised his arms slightly and squinted at them, a carpenter troubled by a burl in the wood.

Kurzweil acknowledges that he was profoundly affected by the early death of his father, Fredric. Fredric was a brilliant conductor and pianist, but he worked incessantly to make ends meet and was often absent from the family. Kurzweil's mother once observed, "It was hard on Raymond. He needed a father—and his father was never around." Kurzweil has preserved fifty boxes of his father's effects, everything from his letters and photographs to his electric bills, all pack-ratted into a storage facility in Newton, Massachusetts. He hopes to someday create a virtual avatar of his father and then populate the doppelgänger's mind with all this information, as well as with his own memories of and dreams about his father, exhuming a Fredric Kurzweil 2.0.

"We have spent millennia rationalizing the tragedy of death—'Oh, it's natural, it's the goal of life,' " Kurzweil told me. "But that's not really how we feel when we hear that someone we love has died." He fell silent, then reverted to the question of how realistic his father's avatar would be, how consoling. "Passing a Fredric Kurzweil Turing test is getting easier and easier," he said, smiling wryly, "because the people who knew him, like me, are getting older and older."

The Meat Puppets, fighting off old age, must contend with evolutionary contingency. Jan Vijg, who co-authored a recent paper arguing that our life span is basically capped at a hundred and fifteen, told me, "Yes, our bodies are information-processing systems. But to fix the body-as-computer requires an in-depth understanding of what's going on in your cells at a molecular level. And we don't even know how many types of cells there are! Creating a human is not nearly as easy as creating an A.I., because we're so very confusingly and *unintelligently* designed by random changes acted upon by natural selection."

The RoboCops must contend with the boundaries of the human terrain. Osman Kibar, the C.E.O. of a biotech company called Samumed, told me, "We humans are very creative. When we hit a biological limit, we cheat—like Kurzweil, who's saying, 'Let's change the definition of human.' As each of our functions is uploaded or replaced, at some point you stop calling that a human and start calling it an A.I." We already have technologies that work inside the body, such as pacemakers and cochlear implants. A paralyzed man recently typed eight words a minute by using a brain-computer interface inserted in his motor cortex. How long will it be before the advantages of scaling and precision manufacture can be applied to the whole body?

The 2045 Institute, started by a wealthy Russian inspired by Kurzweil's time line, believes that we can at least begin making down payments on that moment. The institute's Web site has an "immortality button," which you click "to start the development of your own personalized immortal avatar." You can select from among a remote-controlled robotic copy, a full-body prosthesis topped off by your transplanted head, and a top-of-the-line, wholly artificial body containing your uploaded essence, which will "achieve perfection of form and be no less attractive than the human body."

The sticking point seems to be what to do about our heads, specifically our brains. The futurist Juan Enriquez told me, "We'll be able to transplant a mouse head

within five years. And then it gets really interesting—does Mickey remember Minnie?" At the moment, however, no one has figured out how to refresh Mickey's brain biology, no matter which body it's attached to. Neurons don't regenerate, and we don't grow new ones, except in the hippocampus. Stem cells imported into the brain don't help; they just sit there, then die.

Benjamin Rapoport, a neurosurgery resident at Weill Cornell Brain and Spine Center who's working on a project that would directly connect brains to A.I.s, said, "The question is, What is the fundamental you that is you? Most people feel it's the mind. But can your mind exist only in a biological substrate that weighs 1.5 kilograms, is very wet, and floats like a jellyfish? Or could it conceivably exist someplace else?" In a computer, say. A two-way, high-bandwidth interface with the brain could be available within a decade, and scientists are already trying to map the hundred billion neurons in the brain and the hundred-trillion-plus connections between them—the "connectome," as it's infelicitously called. Currently, you can model someone's brain at the synapse level only by slicing it up after the person is dead. Eventually, however, it seems possible that we could achieve "whole-brain emulation" with live subjects. There would then be permanent copies of our brains that would—we hope—themselves have consciousness.

But would that be us? Even if you set aside the question of what portion of being human is somatic—of how much our identity derives from the tactile and sensory and emotional consequences of being embodied in flesh, rather than in Row D of a server farm—you can't dispense with the problem of memory. Unlike the RAM in a computer, human memories emerge from electrochemical inputs, which trigger your brain to match a pattern and produce an output. There is no physical location for your memory of a first kiss. The recollection changes with the stimulus that triggers it, depending on whether you recall the kiss the next day, read about it in a letter, or run into that old girlfriend twenty years later. So if the connectome project works, and we're transferred to silicon, we might be invulnerable to physical decay and capable of astounding feats of learning and ratiocination, yet shorn of that first memory of crocuses in a spring rain. But maybe we'd have no memory of caring.

Ray Kurzweil and Aubrey de Grey have the same backup plan if the work doesn't advance as quickly as they expect: when they die, they will be frozen in liquid nitrogen, with instructions left to reawaken them once science has finished paving the road to immortality. Their optimism is admirable, and perhaps the anxieties that their blueprints stir up are just the standard resentments of the late

adopters and the left-behinds. "People are daunted when they hear of these things," Kurzweil told me. "Then they say, 'I don't know if I want to live that long.' " For Kurzweil, who has two children, the acceptance of inevitable death is no saner than the acceptance of early death. "It's a common philosophical position that death gives meaning to life, but death is a great robber of meaning," he said. "It robs us of love. It is a complete loss of ourselves. It is a tragedy."

And yet. Last year, the geneticist Nir Barzilai hosted a screening of a documentary about longevity, and afterward he posed a question to the three hundred people in the audience. He told me, "I said, 'In nature, longevity and reproduction are exchangeable. So Choice One is, you are immortalized, but there is no more reproduction on Earth, no pregnancy, no first birthday, no first love'—and I go on and on and on." He laughed, amused by his own determination to load the dice. " 'Choice Two,' I said, 'is you live to be eighty-five and not one day sick, everything healthy and fine, and then one morning you just don't wake up." The vote was decisive, he said. "Choice One got ten or fifteen people. Everyone else raised their hands for Choice Two."

This wish to preserve life as we know it, even at the cost of dying, is profoundly human. We are encoded with the belief that death is the mother of beauty. And we are encoded, too, with the contradictory determination to remain exactly as we are, forever—or at least for just a bit longer, before we have to go. ♦

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