Inquiring Minds Topic – 30 June 2017

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Silicon Valley's Quest to Live Forever

1. **The people who admire themselves, such as Hollywood stars, seem to want to extend that time of adoration for as long as possible. Can they?**
2. **They assume that their brains will remain as young as their bodies. Will they?**
3. **They assume that we will be able to keep working to provide the food all of us will continue to need when we are 150 years old. Will we?**
4. **They assume that no new diseases will crop up due to extended aging. Will they?**
5. **They assume that only the nice people like you and me will live on to benefit our world. It won't be the Hitler types who will live on to continue their destruction. Is that the way it will work?**

- questions provided by Roger Palms who edited for this discussion the article found at **www.newyorker.com**/magazine/2017/04/03/silicon-valleys-quest-to-live-forever

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.

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 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. 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 that if we hack the code correctly, "thermodynamically, there should be no reason we can't defer entropy indefinitely. We can end aging forever."

Martine Rothblatt, the founder of a biotech firm called United Therapeutics, which intends to grow new organs from people's DNA, explained, "Clearly it is possible through technology to make death optional."

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. 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'?"

In the early nineties, research on *C. elegans*, a tiny nematode worm 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. Age went from being a final stage to something avoidable or at least vastly deferrable.

A leading *C. elegans* researcher told me, "At the beginning, we thought it would be simple 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. As we age, our telomeres become shorter and, when these shields go, cells stop dividing. 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.

Aubrey de Grey likes to compare the body to a car: a mechanic can fix an engine without necessarily understanding the physics of combustion. De Grey is the chief science officer of Silicon Valley's SENS Research Foundation, which stands for Strategies for Engineered Negligible Senescence. 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).

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."

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 see troubleshooting all seven pathways through such schemes—and you have to troubleshoot them all for his plan to work—as a foredoomed labor.

The great majority of longevity scientists are healthspanners, not immortalists. They want to give us a healthier life followed by a quick and painless death. 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."

Ned 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.

A systemic approach to aging, which would ideally result in your general practitioner prescribing you a "God pill," is philosophically attractive but financially infeasible. Unity is taking aim at glaucoma, macular degeneration, and arthritis. 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 billionaires eager to stretch our lives, or at least their own, to a span that Thiel has pinpointed as "forever." 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.

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."

Unsurprisingly, it was Google that transformed the Valley's view of aging.
Bill Maris who was in the vanguard as the founder and C.E.O. of Google Ventures, 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. 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. 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.

Another scientist who's familiar with Calico's (the Bill Maris company) workings said that it's pursuing its mission judiciously, but that the company began as a vanity project. The scientist said, "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."

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. 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. "

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. After we've spawned, we're living on time that evolution regards as pointless. 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*."

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.

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, has had injections with stem cells derived from his DNA. He believes that the process has reversed his aging.

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." 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).

Ray Kurzweil subscribes to the belief that the body is essentially a computer made up of over-writable 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 will bring us to longevity escape velocity within about fifteen years.

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 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? 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?

For further consideration: https://muse.jhu.edu/article/621222; https://www.menshealth.co.uk/healthy/brain-training/who-wants-to-live-forever; https://www.theatlantic.com/health/archive/2017/02/should-we-die/516357; https://www.quantumrun.com/article/science-aging-can-we-live-forever-and-should-we; http://www.townandcountrymag.com/society/money-and-power/a9202324/science-of-longevity