

## The anti-aging revolution

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In early 1934, Depression-weary Americans were beginning to see tendrils of hope poking out of the bleak landscape. President Franklin D. Roosevelt's New Deal was bringing the economy back from the dead. Galvanized by the sight of elderly women scrounging for food from garbage, California physician Francis Townsend had launched a crusade for government-funded pensions that would soon spur the creation of Social Security. Things were even looking up for the long-suffering Washington Senators, who had made it to the World Series the previous fall.

But one of the new year's most promising developments passed almost unnoticed. According to a brief article in the Jan. 13 Science News Letter, Cornell University researcher Clive McCay was nearing the end of a four-year study that showed that rats' life spans were greatly extended when they were put on near-starvation diets.

To many of his scientific peers, McCay's data made no sense at all. A glorious new chapter in nutrition science had been opened not long before by the discovery of dietary deficiencies behind scourges such as rickets, pellagra, and beriberi. In the wake of such progress, it seemed almost subversive to suggest that a bunch of rodent Oliver Twists, raised on such short rations that their growth was stunted, could live radically longer than well-fed ones. McCay sheepishly acknowledged in his initial report that his results seemed "little short of heresy."

Over the next several decades, his discovery was all but forgotten outside of the back halls of science -- a laboratory curiosity that

didn't actually spark much curiosity. Most scientists were reluctant to risk wasting time probing an anomaly that seemed as baffling as aging itself.

Calorie restriction (CR), as it's now called, eventually was shown to extend many species' life spans by a third or more. Now that anti-aging research is hot, it seems bizarre that CR spent decades on science's back shelf. Simply put, McCay showed that the rate of aging is incredibly plastic, and that it's supremely simple to brake it in animals whose inner workings aren't all that different from ours. No biomedical discovery of the past century was more astonishing or significant.

So here's a prediction: McCay will someday be recognized as one of the last century's most important discoverers. He wasn't a genius with a capital G. But his skinny rats had made history with a capital H.

The idea of mimicking CR with drugs -- and without the hunger pangs that discourage most people from trying it -- finally got traction in the late 1990s when scientists began getting hints on the kinds of compounds that might work. (It had always been clear that such medicines were needed to make CR's broad health- and longevity-enhancing effects available to the masses, but before then researchers knew too little to get started.) Around 2000 several biotech startups were formed to pursue CR mimetics, including LifeGen Technologies of Madison, BioMarker Pharmaceuticals of San Jose, and GeroScience of Pylesville, Md. This first wave of CR-mimetic companies have been low-profile affairs compared with Sirtris Pharmaceuticals, the Cambridge, Mass., biotech juggernaut formed a few years later to develop drugs based on resveratrol, the famous red-wine compound shown to induce CR-like effects in animals. (Sirtris was acquired by GlaxoSmithKline in 2008.) They haven't been idle, though. GeroScience has worked with Procter & Gamble's (PG, Fortune

500) pet food unit, for example, on CR mimetics for pets, including a sugar in avocados called mannoheptulose. I wouldn't be surprised to see Fido and Muffy launch the era of effective anti-aging medicines.

The startups also deserve credit for beginning to transform the anti-aging quest from a guessing game into a fairly routine exercise in drug development. Before the pursuit of CR mimetics took off, most anti-aging investigators were like blind magicians trying to pull rabbits from a barrel of snakes. Not surprisingly, even the serious scientists among them often wound up covered in snake oil, promoting "breakthroughs" such as monkey-testicle implants and radium-laced elixirs.

CR-mimetic developers don't have to solve the monster problem of how aging happens in order to devise interventions that oppose it. Evolution has solved the problem for them. It did so while fashioning CR's machinery, which is poised to carry out all the intricate metabolic adjustments necessary to brake aging when activated by a true CR mimetic. Such drugs will be designed to switch on an ancient, enormously complex mechanism embedded in our genomes to postpone, and possibly attenuate, a myriad of ills brought on by aging: dementia, heart disease, cancer, as well as wrinkles, arthritis, age-related loss of muscle and bone, and the onset of senior moments. In effect, they'll represent the biggest free lunch in medical history. And given that compounds capable of emulating key effects of CR in rodents have already come to light, it's arguable that the Great Free Lunch's appetizers are now on the table.

Just a few weeks before his death in 1996 at age 100, George Burns was still enjoying life, cracking wise at a Christmas party thrown by Frank Sinatra. France's Jeanne Calment, who holds the record for longevity (she died in 1997 at 122), was similarly droll and unsinkable. When a reporter at an annual party in her honor

departed with the words "Until next year, perhaps?" she shot back, "I don't see why not! You don't look so bad to me."

Very old people with such élan are obviously rare. But I suspect that many who retain mental clarity in late life make their way toward something like Burns' and Calment's radiant rapprochement with old age. Surveys show that self-reported happiness among older people in reasonably good health is generally higher than among younger groups. I don't want to sugarcoat old age -- it isn't for sissies, as they say. But I'd love to see more well-tempered sages like Burns in the world. Call it the George Burns scenario.

Some critics argue that developing anti-aging drugs is likely to engender a disastrous surfeit of needy oldsters gripped by greed and ennui. Leon Kass, a University of Chicago professor who chaired the President's Council on Bioethics under George W. Bush, has asserted, for instance, that "the desire to prolong youthfulness [is] an expression of a childish and narcissistic wish incompatible with devotion to posterity." Some naysayers add that "greedy geezers" will rack up ruinous Medicare and Social Security bills. Worse, they argue, the drugs may simply drag out late-life morbidity, recreating en masse something like the Greek myth of Tithonus, who was granted eternal life but not everlasting youth and wound up miserably withered forever.

I regard such visions as ill-founded. For one thing, there's evidence that CR mimetics would buy us quality time, not prolong misery. A study of CR's effects in rhesus monkeys has shown that it reduces age-related diseases by about a third in the primates during their later lives -- the calorie-restricted monkeys have greater lean muscle mass, significantly less age-related brain atrophy, half as much cancer, and half as much cardiovascular disease as do peers on normal diets. The world's longest-lived human population, natives of Japan's Okinawa prefecture, whose

scant traditional diets are regarded as tantamount to mild CR, have 80% less breast and prostate cancer at advanced ages than North Americans do, suffer about 40% fewer hip fractures, and experience half the rate of dementia between 85 and 90.

It's possible that anti-aging drugs would compress late-life misery, letting us reach a ripe old age in good shape before a speedy demise. That could have huge economic and social payoffs -- much greater, for instance, than a miracle cure for all cancers.

Even if the medicines only postponed aging's deterioration, boosting life expectancy by, say, a decade, the benefits would be monumental. As Richard Miller, a University of Michigan gerontologist, says, "When you ask people, 'Would you like to live to 100?' they picture what today's elderly, infirm person looks and feels like. But the proper question is a different one: 'Would you like to add another 10 or 20 years to the middle of your life, so you reach 80 or 90 in the same condition that people generally are today at around 60 or 70?' "

A drug that increases healthy life-years would deliver large benefits across many sectors of the economy. Healthier, longer-living people can stay in the workforce longer, preserving skilled human capital that might otherwise be lost. Healthier workers are physically and mentally more robust, making them more productive. They're motivated to invest more in developing their skills, because they expect to reap the benefits of such investments for longer periods. They save more for retirement, boosting capital formation that fuels economic growth. They pose lighter burdens on federal entitlement programs and contribute more in federal and state tax revenue. Such factors probably explain why per-capita incomes of nations around the world have long risen in tandem with their populations' life expectancies.

Anti-aging drugs may well have downsides too. For instance, nest

eggs that once seemed adequate may prove too small in an era of extended life spans. But the drugs should also help with that problem by keeping us vibrant enough to work after 62, the average age at which U.S. workers have retired in recent years. Of course, it remains to be seen whether the economy will support demand for older workers' services. Still, surveys show many baby boomers expect to work at least part-time in retirement for both fiscal and personal-fulfillment reasons -- they apparently agree with a piece of wisdom George Burns expressed late in life: "As long as you're working, you stay young."

Where does the anti-aging quest stand? As always with cutting-edge science, the quest has had ups and downs. In 2008, Harvard's David Sinclair and colleagues reported that resveratrol failed to extend the life spans of mice on normal diets, suggesting that it is at best a partial CR mimetic -- the group had earlier made a splash by showing that the compound induces CR-like effects in mice on high-fat diets. But last year a major turning point was reached: Researchers showed for the first time that a drug could convincingly extend life span in mammals.

The drug was rapamycin, a medicine long prescribed to help prevent rejection of transplanted organs. In parallel mouse experiments in three different labs, scientists funded by the National Institute on Aging found that rapamycin dramatically boosted longevity in mice on normal diets in a way reminiscent of CR's effects. Stunningly, the study showed that when rodents were first put on the drug at 20 months of age, roughly equivalent to 60 years in humans, the life expectancies of males were boosted by 28%, and that of females by 38%. Even CR itself hasn't been shown to exert such large effects on animals so close to the end of their lives. Former perma-bears about the anti-aging quest are now sounding upbeat.

Unfortunately, the drug industry has shown little interest in trying

to translate such breakthroughs into anti-aging medicines. Both drug regulators and the medical establishment still essentially view aging as totally mysterious, inexorable, and intractable -- they wouldn't dream of adding it to the official list of drug indications. Thus, drug companies have no way to develop anti-aging compounds as high-margin prescription drugs. And that means that spending many hundreds of millions of dollars on clinical trials of the drugs' efficacy just doesn't compute. (The relatively small proceeds from marketing them as low-margin dietary supplements can't justify such costly, high-risk trials either.)

Besides, vetting the drugs would require first developing reliable biomarkers of aging, telltale signs of normal bodily decline over time that could be used to register how fast people are going downhill. Such biomarkers would enable the vetting of CR mimetics' efficacy in trials that last only a few years, rather than the impossibly long time it would take to assess their longevity-boosting effects in humans.

In short, the hugely promising anti-aging quest is now stuck between the R and the D stages, and I fear it will stay there until the federal government greatly steps up funding in the area. I, for one, don't plan to take purported CR mimetics until there's some reasonably rigorous clinical trial data showing that they're safe and effective. And until such data are available, the anti-aging revolution is likely to remain little more than the enthusiastic pursuit of placebo effects by wishful thinkers.

All this is terribly ironic. In effect, it means that authorities charged with promoting public health are fatalistically standing and watching the "silver tsunami" of population aging -- with its huge economic and human costs -- bearing down on us as if there were no way to shelter ourselves from its full force. Meanwhile, the authorities are perfectly willing to devote many billions of

dollars annually to the pursuit of ever costlier palliatives for diseases of aging, which are typically applied when it's too late to do much good -- the federal government now annually spends less than 0.04% as much on research about the biology of aging as it does on Medicare.

So here's the moral of the story: The George Burns scenario is within our grasp if we collectively recognize what has happened in aging science and seize the day. And while anti-aging drugs may not enable all of us to live as long as Burns, they promise to let many of us age as gracefully as he did and thus aspire to our own version of his timelessness. As Burns once quipped, "You can't help getting older, but you don't have to get old." Words to remember from a wise guy to the end.