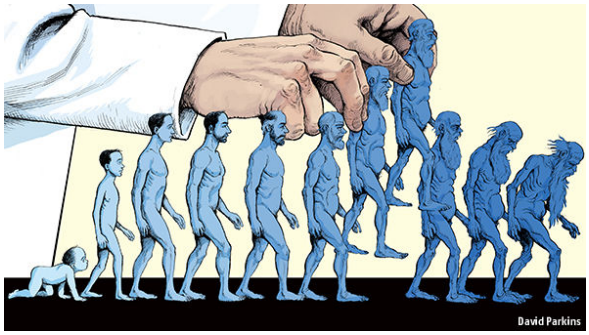
The Economist

Longevity

Adding ages

The fight to cheat death is hotting up

Aug 13th 2016



MICHAEL RAE eats 1,900 calories a day, 600 fewer than recommended. Breakfast is a large salad, yogurt and a "precisely engineered" muffin. In a mere 100 calories this miracle of modern gastronomy delivers 10% of Mr Rae's essential nutrients. Lunch is a legume-based stew and another muffin. Dinner varies. Today he is looking forward to Portobello mushroom with aubergine and sage. There will be a small glass of red wine. He has been constraining his diet this way for 15 years.

In some animals calorie restriction (CR) of this kind seems to lessen the risk of cancer and heart disease, to slow the degeneration of nerves and to lengthen life. Mr Rae, who works at an anti-ageing foundation in California, thinks that if what holds for rodents holds for humans CR could offer him an extra seven to 15 years of healthy life. No clinical trials have yet proved this to be the case. But Mr Rae says CR dieters have the blood pressure of ten-year-olds and arteries that are clean as a whistle.

The "profound sense of well-being" Mr Rae reports might seem reward enough for his privations. But his diet, and the life extension he thinks it might bring, are also a means to an end. Mr Rae, who is 45, thinks radical medical advances that might not merely slow but stop, or reverse, ageing will be available in the not-too-distant future. If CR gets him far enough to benefit from these

marvels then a few decades of deprivation might translate into additional centuries of life. He might even reach what Dave Gobel, boss of the Methuselah Foundation, an ageing-research charity, calls "longevity escape velocity", the point where life expectancy increases by more than a year every year. This, he thinks, is the way to immortality, or a reasonable approximation thereof.

That all remains wildly speculative. But CR is more than just an as-yet-unproven road to longer human life. Its effects in animals, along with evidence from genetics and pharmacology, suggest that ageing may not be simply an accumulation of defects but a phenomenon in its own right. In a state of nature this phenomenon would be under the control of genes and the environment. But in a scientific world it might in principle be manipulated, either through changes to the environment (which is what CR amounts to) or by getting in among those genes, and the metabolic pathways that they are responsible for, with drugs.

A treatment based on such manipulation might improve the prospects of longer and healthier life in ways that drugs aimed at specific diseases cannot match. Eileen Crimmins, a researcher at the University of Southern California in Los Angeles, points to calculations which show that the complete elimination of cardiovascular disease would add only 5.5 years to overall life expectancy in America, and removing deaths from cancer would add just 3.2 years. This is because diseases compete to kill people as they age; if one does not get you the next will. According to Dr Crimmins, increasing life expectancies much beyond 95 would require an approach that held the whole pack at bay, not just one particular predator.

Something which slowed ageing down across the board might fit the bill. And if it delays the onset of a range of diseases it might also go some way to reducing the disability that comes with age. An ongoing long-term study at Newcastle University has been looking at the health and ageing of nearly 1,000 subjects now aged 85. At this point they have an average of four to five health problems. None of them is free from disease. Most researchers in the field scoff at talk of escape velocities and immortality. But they take seriously the prospect of healthier 85 year olds and lifespans lengthened by a decade or so, and that is boon enough.

Indications of immortality

Before discovering whether anti-ageing drugs might be able to deliver such things, though, researchers need to solve a daunting regulatory conundrum. At the moment the agencies that allow drugs to be sold do not consider ageing *per se* to be an "indication" that merits therapy. It is, after all, something that happens to everyone, which makes it hard to think of as a disease in search of a cure, or even a condition in need of treatment. Unless ageing is treated as an indication, anti-ageing drugs can't get regulatory approval. And there's little incentive to work on drugs you can't sell.

If regulators were to change their stance, though, the interest would be immense. A condition that affects everyone is as big a potential market as can be imagined. And there are hints that the stance may indeed be changing. Two existing drugs approved for other purposes—metformin, widely used and well tolerated as a treatment for diabetes, and rapamycin, which reduces the risk of organ transplants being rejected—look to some researchers as though they might have broad anti-ageing effects not unlike those claimed for CR. In 2014 a study of 90,000 elderly patients with type 2

diabetes found that those receiving metformin had higher survival rates than matched non-diabetic controls. Other work has shown its use is associated with a decreased risk of cancer.

Scientists at the Institute for Ageing Research at the Albert Einstein College of Medicine, in New York, want to mount a trial of metformin in elderly subjects to see whether it delays various maladies (and also death). If that turns out to be the case, it will go a long way to showing that there is a generalised ageing process that can be modulated with drugs. Nir Barzilai, one of the researchers involved, says an important reason to do the trial is to have an indication against which next-generation ageing drugs can be assessed by regulators.

This sort of interest seems to be triggering a change of tone at America's Food and Drug Administration over whether it might approve an anti-ageing drug. The regulator is thinking about when a broad, and so far unprecedented, claim of anti-ageing might be considered to be supported by the evidence; it is "looking forward to seeing this area of science evolve". In the dry language of a government agency these are encouraging words.

If an unregulated diet can do the trick, why does the world need drugs? Three reasons. One is that taking a few pills a day will be easier for most than subsisting on low-calorie muffins and salad. A second is that companies can make money making pills and will compete to create them. A third is that pills may work better than diets. Dr Barzilai, who is in the pill camp, points out that CR works less well in primates than other mammals, and that people with low body-mass indices, a natural condition for those restricting their calories, are in general more likely to die. Those who do well on CR, he says, are likely to be a subset benefiting from the right genetic make-up. His hope is that a range of targeted therapies might allow everyone to get the benefits.

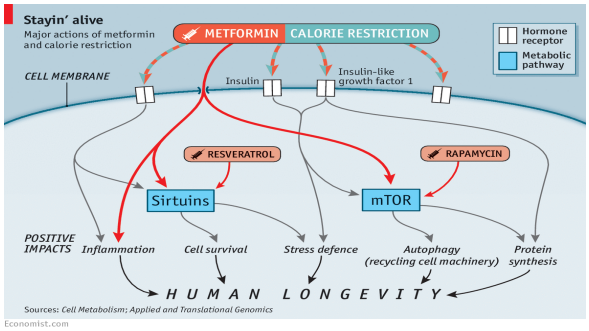
If they do, it will be by inducing changes in metabolism. It has been known for 20 years that altering the gene daf-2 in roundworms slows their ageing and doubles their lifespans; another gene, daf-16, is now known to be required for this to work. Equivalent genes in humans are in charge of the cell-surface receptors for insulin and insulin-like growth factor 1, hormones with key metabolic roles. The human equivalent of daf-2 seems to be turned on by CR. Very long-lived people have been found to share particular variants of the human version of daf-16.

Another effect of CR is that it deactivates mTOR, a protein that helps pass signals from growth hormones to the parts of the cell involved in protein synthesis. It plays a role in regulating the cell's metabolism, division and growth, and prevents the breakdown of damaged cells. When food is abundant mTOR stimulates cell division and growth.

Throwing the switch

These lines of research suggest that in the animals where CR works well it switches cells from a regime where they concentrate on growing to one where they concentrate on their own repair. In that second mode damage to cells accumulates more slowly, which means they age less. Drugs that seem to have an effect on ageing achieve some of the same shift. Metformin acts on a number of hormone receptors which are also affected by CR (see chart); rapamycin works on a pathway that gets its name from a protein that is the "target of rapamycin": mTOR. Reducing the function of

mTOR extends life in yeast, worms and flies. In 2009, work in a number of laboratories showed that rapamycin can extend the lifespan of middle-aged mice by 14%.



Alexander Zhavoronkov, the boss of Insilico Medicine, a longevity firm, says he is testing rapamycin on himself (self experimentation does not seem uncommon in the field). But he warns it is necessary to have a significant knowledge of biomedicine to do so safely. The drug has serious side effects; rodents treated with it suffer from insulin resistance and it suppresses the immune system. That's good when preventing the rejection of organ transplants—the drug's current medical use—but not so good in otherwise healthy people. One idea is that low doses might preserve the drug's benefits while limiting its side-effects.

There are other drugs, though, that target the same pathway with fewer downsides. One of these, resveratrol, caused a great deal of excitement among longevity researchers a few years ago because it kept mice on rich diets youthful. A lot of the initial interest has waned since it was discovered to be less helpful in mice that are not overweight, but it is still being investigated as an Alzheimer's treatment.

David Sinclair of the Harvard Medical School, who was part of the initial enthusiasm, describes it as a "dirty" drug, in that it has a number of targets within the cell. Among them are a set of proteins known as sirtuins which appear to be activated by resveratrol. Dr Sinclair created a company, Sirtris Pharmaceuticals, to investigate the potential of drugs aimed at these targets. GSK, a British pharma company which bought Sirtris in 2008, continues this work, though to date it has not yielded as much as was once hoped.

Sirtuins may act as metabolic sensors, and a number are found exclusively in the mitochondria, the structures in cells that look after respiration and which are central to the evolving concept of cellular ageing. Thomas von Zglinicki of Newcastle University says ageing cells are characterised by mitochondrial damage and have difficulty recycling damaged or broken cell machinery. They produce pro-inflammatory factors called cytokines which move neighbouring cells to senescence; chronic progressive inflammation of this sort drives various age-related diseases.

João Passos, also at Newcastle University, says cells from which mitochondria are removed start to look more like young cells and stop secreting cytokines. Other work has shown that killing off mitochondria can mimic some of the effects of drugs that activate mitochondrial renewal—such as rapamycin. Faster turnover of mitochondria seems to improve their functioning.

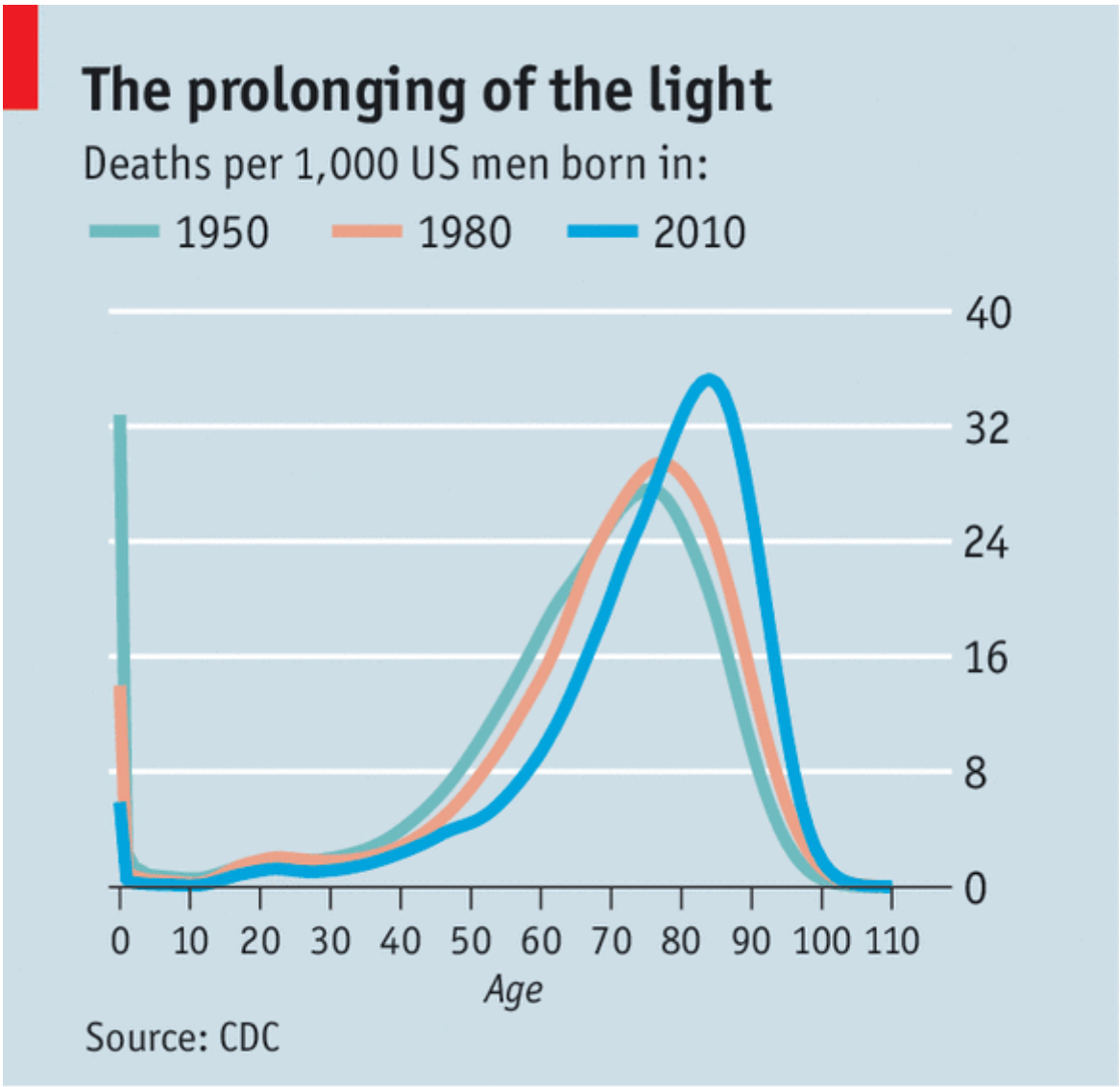
Data against death

Such discoveries in cell and molecular biology have perked up commercial interest in longevity. So too has data from the hundreds of thousands of human genome sequences. Dr Zhavoronkov's Insilico Medicine, based in Baltimore, is using machine learning on vast piles of published genomic data to work out the differences between the tissues of young and old people and to look at how

patterns of gene expression evolve as people age. It then looks in drug databases for molecules that might block the effects of the genes it thinks matter.

The force to be reckoned with in this field, though, is Craig Venter, a pioneer in gene sequencing. In 2013 he founded Human Longevity Inc (HLI), based in San Diego. Like Insilico, HLI wants to sift through genomic data; but it does so on a vastly larger scale, generating the genomic data itself and matching them with details of physiology and appearance. Dr Venter hopes this will allow the company to unpick the genetics of longevity and predict how long people will live. Research at HLI has already found that some genetic variations are absent in older people, a finding that implies they might be tied to shorter lifespans. Companies such as Celgene and AstraZeneca that work in drug discovery have made deals to collaborate with HLI. Dr Venter says HLI may eventually move into the drug business itself.

For those who cannot wait for drugs, HLI has a high-end "wellness" service called the Health Nucleus. At prices starting from $25,000 it will give a customer a



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constellation of cutting-edge tests, including a full sequence of both his genome and a battery of tests for the signs of cancer, Alzheimer's and heart disease. Lots of tests means lots of possibilities for "false-positive" results; but the affluent clients of Health Nucleus may worry less about follow-ups that reveal false alarms than other people do.

In 2013 Google (now Alphabet) started a venture called the California Life Company, or Calico, to take a "moonshot" approach to anti-ageing; the company has said it will invest up to $750m in the venture. Calico is a drug-development company much more willing to talk about its world-leading scientists, such as Cynthia Kenyon, a worm biologist, and the track record of its boss, Arthur Levinson, who used to run Genentech, a biotech giant, than about what it is actually doing. But it has announced a series of collaborations, the most significant of which is a ten-year R&D deal with AbbVie, a pharma company based in Chicago, focused on cancers and degenerative nerve conditions.

Degeneration leads to thoughts of regeneration. Even the most enthusiastic adherents of slowing down ageing by means of diet or pharmacology have to admit that it will not keep people going forever. At best it might allow them to age as slowly as the slowest-ageing people do naturally. And that makes it unlikely, even at its most effective, to increase lifespans beyond 120, because that seems to be more or less the natural upper limit to a human lifespan. Improvements in medicine and welfare mean that there are many more people in their 90s and 100s round the world today than there used to be. The number of people in their 130s, though, remains stubbornly at zero.

To do something about this means not just slowing ageing but stopping or reversing it, either by causing bits of the body to rejuvenate themselves or by removing and replacing them. This is where stem cells come in. They play an important role in the repair and regeneration of tissue; they can be induced to differentiate into a range of specialised cells, and thus to replace cells that are worn out or used up. Regenerative therapies seek to supplement this repair using stems cells from elsewhere. They might be taken from frozen samples of placentas; they might be created from existing body cells.

Many stem-cell therapies are moving rapidly towards clinical trials under the rubric of "regenerative medicine". Both Calico and HLI are active in the field. Research has shown that nerve cells grown from human embryonic stem cells and transplanted into rats with the equivalent of Parkinson's disease proliferate and start to release dopamine, which is what such rats and people lack. Roger Barker of the University of Cambridge recently treated a man with Parkinson's this way. ReNeuron, based in Bridgend in Wales, is in trials designed to discover the efficacy of stem cells as a treatment for disabilities brough on by stroke. Despite the risks of unregulated therapies, hundreds of clinics around the world are already rushing to offer "treatments" for the diseases of age. This is unsurprising. It is historically an area rich in hope, hype and quackery, and it will take some time for well-founded research to clean the stables—if, indeed, it can.

Another regenerative possibility flows from studies which find signs of rejuvenation in elderly animals exposed to the blood of younger animals. Infusions of young people's blood plasma are being tried out on some Alzheimer's patients in California. A startup called Ambrosia, based in Monterey, recently began "trials" of such a therapy with healthy participants who pay $8,000 to take part; critics say they are so lacking in controls that they are unlikely to generate any useful information. If particular genes are

beneficial then gene therapy, or gene editing, could prove to be fertile ground; work to this end has begun in mice. And some won't wait. Elizabeth Parrish, the boss of a biotech company called BioViva, claims she has already given herself an anti-ageing gene therapy.

Beyond this horizon

The extent to which any of this technology will help will depend on how old those it is used on are when it comes into its own. The scope for radically changing the lifespan of a 65-year-old is much smaller than that of a 20-year-old, let alone an embryo. But the amount that is lost by getting things wrong goes up in exactly the same way.

The idea that radical biotechnology can lead to longer lifespans than that of Jeanne Calment, a French woman whose recorded lifespan of 122 years has never been bettered, seems at best a plausible speculation. To say—as Aubrey de Grey, a noted cheerleader for immortality, has done—that the first person to live to 1,000 has probably already been born seems utterly outlandish. But thinking through Calment's life might give you pause. When she was born, in 1875, the germ theory of disease was still a novelty and no one had ever uttered the word "gene". When she died in 1997 the human genome was almost sequenced. All of modern medicine and psychiatry, barring general-purpose anaesthesia, was developed during her lifetime. If a little girl born today were to live as long—and why should she not?—she would see the world of 2138. The capabilities of medicine at that point will surely still be limited. But no one can guess what those limits will be.

This article appeared in the Briefing section of the print edition