Abolishing ageing

How to live forever

It looks unlikely that medical science will abolish the process of ageing. But it no longer looks impossible

“IN THE long run,” as John Maynard Keynes observed, “we are all dead.” True. But can the short run be elongated in a way that makes the long run longer? And if so, how, and at what cost? People have dreamt of immortality since time immemorial. They have sought it since the first alchemist put an elixir of life on the same shopping list as a way to turn lead into gold. They have written about it in fiction, from Rider Haggard's “She” to Frank Herbert's “Dune”. And now, with the growth of biological knowledge that has marked the past few decades, a few researchers believe it might be within reach.

To think about the question, it is important to understand why organisms—people included—age in the first place. People are like machines: they wear out. That much is obvious. However a machine can always be repaired. A good mechanic with a stock of spare parts can keep it going indefinitely. Eventually, no part of the original may remain, but it still carries on, like Lincoln's famous axe that had had three new handles and two new blades.

The question, of course, is whether the machine is worth repairing. It is here that people and nature disagree. Or, to put it slightly differently, two bits of nature disagree with each other. From the individual's point of view, survival is

an imperative. You cannot reproduce unless you are alive. A fear of death is a sensible evolved response and, since ageing is a sure way of dying, it is no surprise that people want to stop it in its tracks. Moreover, even the appearance of ageing can be harmful. It reduces the range of potential sexual partners who find you attractive—since it is a sign that you are not going to be around all that long to help bring up baby—and thus, again, curbs your reproduction.

The paradox is that the individual's evolved desire not to age is opposed by another evolutionary force: the disposable soma. The soma (the ancient Greek word for body) is all of a body's cells apart from the sex cells. The soma's role is to get those sex cells, and thus the organism's genes, into the next generation. If the soma is a chicken, then it really is just an egg's way of making another egg. And if evolutionary logic requires the soma to age and die in order for this to happen, so be it. Which is a pity, for evolutionary logic does, indeed, seem to require that.

The argument is this. All organisms are going to die of something eventually. That something may be an accident, a fight, a disease or an encounter with a hungry predator. There is thus a premium on reproducing early rather than conserving resources for a future that may never come. The reason why repairs are not perfect is that they are costly and resources invested in them might be used for reproduction instead. Often, therefore, the body's mechanics prefer lash-ups to complete rebuilds—or simply do not bother with the job at all. And if that is so, the place to start looking for longer life is in the repair shop.

Seven deadly things

One man who has done just that is Aubrey de Grey. Dr de Grey, who is an independent researcher working in Cambridge, England, is a man who provokes strong opinions. He is undoubtedly a visionary, but many biologists think that his visions are not so much insights as mischievous mirages, for he believes that anti-ageing technology could come about in a future that many now alive might live to see.

Vision or mirage, Dr de Grey has defined the problem precisely. Unlike most workers in the field, he has an engineering background, and is thus ideally placed to look into the biological repair shop. As he sees things, ageing has seven components; deal with all seven, and you stop the process in its tracks. He refers to this approach as strategies for engineered negligible senescence (SENS).

The seven sisters that Dr de Grey wishes to slaughter with SENS are cell loss, apoptosis-resistance (the tendency of cells to refuse to die when they are supposed to), gene mutations in the cell nucleus, gene mutations in the mitochondria (the cell's power-packs), the accumulation of junk inside cells, the accumulation of junk outside cells and the accumulation of inappropriate chemical links in the material that supports cells.

It is quite a shopping list. But it does, at least, break the problem into manageable parts. It also suggests that multiple approaches to the question may be needed. Broadly, these are of two sorts: to manage the process of wear and tear to slow it down and mask its consequences, or to accept its inevitability and bring the body in for servicing at regular intervals to replace the worn-out parts.

Eat up your greens

Managing wear and tear may not be as complicated as it looks, for the last five items on Dr de Grey's list seem to be linked by a single word: oxidation. Regular visitors to the “health and beauty” sections of high-street pharmacies will, no doubt, have come across creams, pills and potions bearing the word antioxidant on their labels and hinting—though never, of course, explicitly saying—that they might possibly have rejuvenating effects. These products are the bastard children of a respectable idea about one of the chief causes of ageing: that one big source of bodily wear and tear, at least at the chemical level, is the activity of the mitochondria.

Mitochondria are the places where sugar is broken down and reacted with oxygen to release the energy needed to power a cell. In a warm-blooded creature such as man, a lot of oxygen is involved in this process, and some of it goes absent without leave. Instead of reacting with carbon from the sugar to form carbon dioxide, it forms highly reactive molecules called free radicals. These go around oxidising—and thus damaging—other molecules, such as DNA and proteins, which causes all sorts of trouble. Clear up free radicals and their kin, and you will slow down the process of ageing. And the chemicals you use to do that are antioxidants.

This idea goes back to one of the founders of scientific gerontology, Bruce Ames of the University of California, Berkeley. Dr Ames began his career studying cancer. He found that damage to certain genes was a cause of cancer. These genes evolved to keep tumours at bay by stopping cells dividing too

readily, and the damage was often done by oxidation. Gradually, his focus shifted to the more general damage that oxidation can do—and what might, in turn, be done about it.

Some vitamins, such as vitamin C, are antioxidants in their own right. This is the basis of the high-street propaganda, though there is no evidence that consuming such antioxidants in large quantities brings any benefit. A few years ago, however, Dr Ames found he could pep up the activity of the mitochondria of elderly rats—with positive effects on the animals' memories and general vigour—by feeding them two other molecules: acetyl carnitine and lipoic acid. These help a mitochondrial enzyme called carnitine acetyltransferase to do its job. Boosting their levels seems to compensate for oxidative damage to this enzyme. He also reviewed the work of other people and found about 50 genetic diseases caused by the failure of one enzyme or another to link up with an appropriate helper molecule. Such helpers are often B vitamins, and the diseases were often treatable with large doses of the appropriate vitamin.

The enzyme damage in these diseases is similar to that induced by oxidation, so Dr Ames suspects that its effects, too, can be ameliorated by high doses of vitamins. He has gathered evidence from mice to support this idea, but whether it is the case in people has yet to be tested. Nor is it easy to believe it ever will be. The necessary clinical trials would be long-winded. They would also be expensive—and there is no reason for vitamin companies to pay for them since sales are already buoyant and the products could not be patented. Nor is Dr Ames claiming vitamins will make you live longer than a natural human lifespan, even if he thinks they might prolong many individual lives. For that, other technologies will need to be invoked.

Stemming time's tide

One way that might let people outlive the limit imposed by disposable somas is to accept the machine analogy literally. When you take your car to be serviced or repaired, you expect the mechanic to replace any worn or damaged parts with new ones. That, roughly, is what those proposing an idea called partial immortalisation are suggesting. And they will make the new parts with stem cells.

The world has heard much of stem cells recently. They come in several varieties, from those found in embryos, which can turn into any sort of body cell, to those whose destiny is constrained to becoming just one or a few sorts of cell. The thing about stem cells of all types, which makes them different

from ordinary body cells, is that they have special permission to multiply indefinitely.

For a soma to work, most of its component cells have to accept they are the end of the line—which, given that that line in question stretches back unbroken to the first living organisms more than 3 billion years ago, is a hard thing to do. There are, therefore, all sorts of genetic locks on such cells to stop them reproducing once they have arrived at their physiological destination. If these locks are picked (for example by oxidative damage to the genes that control them, as discovered by Dr Ames), the result is unconstrained growth—in other words, cancer. One lock is called the Hayflick limit after its discoverer, Leonard Hayflick. This mechanism counts the number of times a cell divides and when a particular value (which differs from species to species) is reached, it stops any further division. Unless the cell is a stem cell. Every time a stem cell divides, at least one daughter remains a stem cell, even though the other may set off on a Hayflick-limited path of specialisation.

Some partial immortalisers seek to abolish the Hayflick limit altogether in the hope that tissue that has become senescent will start to renew itself once more. (The clock that controls it is understood, so this is possible in principle.) Most, though, fear that this would simply open the door to cancer. Instead, they propose what is known as regenerative medicine—using stem cells to grow replacements for tissues and organs that have worn out. The most visionary of them contemplate the routine renewal of the body's organs in a Lincoln's axish sort of way.

In theory, only the brain could not plausibly be replaced this way (any replacement would have to replicate the pattern of its nerve cells precisely in order to preserve an individual's memory and personality). Even here, though, stem-cell therapists talk openly of treating brain diseases such as Parkinson's with specially grown nerve cells, so some form of partial immortalisation might be on the cards. But it is a long way away—further, certainly, than Dr Ames's vitamin therapy, if that is shown to work.

Neither prevention, nor repair, is truly ready to roll out. But there is one other approach, and this is based on the one way of living longer that has been shown, again and again, in animal experiments, to be effective. That is to eat less.

From threadworms to mice, putting an animal on a diet that is near, but not quite at, starvation point prolongs life—sometimes dramatically. No one has done the experiment on people, and no one knows for sure why it works. But it

does provide a way of studying the problem with the reasonable hope of finding an answer.

Gluttons for punishment

You would, of course, have to wish a lot for a long life to choose to starve yourself to achieve it. Extrapolating from the mouse data, you would need to keep your calorie intake to three-quarters of the amount recommended by dieticians. That means about 1,800 for sedentary men and 1,500 for sedentary women. But several people are trying to understand the underlying biology, in order to develop short cuts.

One such is David Sinclair of Harvard University. Unlike those trying to fight the causes of ageing or to repair the damage done, Dr Sinclair thinks he has found, in caloric restriction as the technique is known, a specifically evolved natural anti-ageing mechanism that is quite compatible with disposable-soma theory.

The reason for believing that prolonged life is an evolutionary response to starvation rather than just a weird accident is that when an animal is starving the evolutionary calculus changes. An individual that has starved to death is not one that can reproduce. Even if it does not die, the chance of it giving birth to healthy offspring is low. In this case, prolongation of life should trump reproduction. And that is what happens, even among people. Women who are starving stop ovulating. The billion-dollar trick would be to persuade the body it is starving when it is not. That way people could live longer while eating normally. They might even, if the mechanism can truly be understood, be able to reproduce, as well.

In Dr Sinclair's view, the way caloric restriction prolongs life revolves around genes for proteins called sirtuins. Certainly, these genes are involved in life extension in simple species such as threadworms and yeast. Add extra copies of them to these organisms' chromosomes, or force the existing copies to produce more protein than normal, and life is prolonged. This seems to be because sirtuins control the abundance of a regulatory molecule called nicotinamide adenine diphosphate which, in turn, controls the release of energy in the mitochondria.

The most intriguing connection in this story is with the French paradox. This is the fact that the French tend to eat fatty diets rich in red meat but to have the survival characteristics of those whose diets are lean and vegetarian. Some researchers link this with their consumption of red wine—and, in particular, of

a molecule called resveratrol that is found in such wine. Resveratrol activates sirtuins, and some similar molecules activate them much more. It is these sirtuin super-stimulators that interest Dr Sinclair.

Not everyone is convinced, but Dr Sinclair has done experiments on mice that look promising, and has started a company called Sirtris Pharmaceuticals to follow it up. The fact that he is (at least in his own eyes) working with nature rather than against it argues that this is the most promising approach of all.

That said, the logic of the disposable-soma theory is profound. Even working with its grain may do no more than buy a few extra years of healthy living. Dr de Grey's reason for thinking that some people now alive may see their lives extended indefinitely is based on the hope that those few extra years will see further discoveries and improved life-extension technologies based on them — a process he describes as achieving “longevity escape velocity”.

The chances are that it will not work. But hope springs eternal. To end with another quote, this time from Woody Allen, “I don't want to achieve immortality through my work. I want to achieve immortality through not dying.” If any researcher manages to beat evolutionary history and achieve his goal, he might get to do both.

The Methuselah mouse

Eyes on the prize

Not so much designing a better mousetrap as designing a better mouse

TO ENCOURAGE people to take his ideas seriously, Aubrey de Grey, the originator of the strategies for engineered negligible senescence, has organised a competition. He is offering a prize for the development of what he calls a Methuselah mouse.

There are actually two prizes to be had. One is for longevity, the other for rejuvenation. The prize for longevity can be won by a new strain of mouse—one bred or genetically engineered to live a long time. That for rejuvenation requires treatment to begin when the mice are already in middle age.

Unlike other engineering prizes (for example, the X Prize for lunar exploration), an award of the Methuselah mouse prize is not the end of the matter. The winner establishes a record that others have to break. At the moment the records for longevity and rejuvenation are five years and almost four in an animal that normally lives for three.

How translatable the lesson of a Methuselah mouse will be to people is a matter of debate. The logic of disposable-soma theory (see article) applies to both species. But that theory also explains their different lifespans. The reason mice age rapidly is that they have lots of predators and would get killed quickly anyway. Humans have few predators and tend not to get killed—at least not as easily as mice. It is therefore worthwhile for people to evolve better repair mechanisms than mice, and thus to age more slowly.

The rate at which an animal aged was once believed to be related to its size. Small animals have faster metabolisms, so it was thought they would wear out more quickly. That relationship, however, is just a coincidence caused by the fact that small beasts usually have more predators than large ones do. If they do not, as for some species of bat, then even a small creature can live for decades in just the way that a large animal would. For this reason, it is difficult to draw firm conclusions about human ageing from mice, even Methuselah mice. The repair mechanisms in the two species may be different.

In the Methuselah mice that exist today, the rejuvenation prize is held by a mouse on a calorie-restricted diet (see article). The longevity prize is held by an animal that could not make the receptor molecule for growth hormone and was thus a fraction of the size of normal mice. One explanation for this mouse's abnormally long lifespan is that slower growth allows for “higher fidelity” growth, with better error-correction during development. The result would be a mouse that is born with less congenital damage and which thus takes longer to accumulate enough further damage to kill it.