Forever young

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THIRTY miles north of San Francisco, on a hillside off highway 101, a cluster of white limestone buildings rises against a blue sky. The architect, I. M. Pei, also designed the Louvre pyramid, and the $50 million it took to put up the buildings came from the trust of a long-dead philanthropist called Beryl Buck.

It's clean-edged, stylish and, depending on your point of view, either an inspired monument to human optimism or the 21st-century equivalent of Canute's seaside throne. Somewhere down one of its airy, sanitised corridors, technicians in white coats are feeding mice experimental drugs—not to cure them of any disease, but in a bid to slow down the rate at which they grow old and die.

Fountain-of-youth recipes of the monkey gland and sleep-with-a-virgin variety are as old and as disreputable as human gullibility itself. But the mice at the Buck Institute for Age Research can count themselves lucky. The compounds in their feeding bowls have impeccable scientific credentials. Codenamed EUK-8 and EUK-134, but more generally known as catalytic scavengers, they're the products of years of lab work.

Last September the drugs rocketed to front-page stardom after scientists fed them to nematode worms. The worms lived a whopping 50 per cent longer than normal. Better still, no voodoo logic was required to explain why. The compounds seemed to work by destroying free radicals, the famous oxidising—and potentially ageing—toxins that virtually all cells create as they burn calories.

But of course people are not big worms—so what are the odds on these scavengers working for us? Frustratingly, the Buck Institute's lips are firmly sealed on how its mice are doing. And maybe that isn't surprising. For thousands of years we've sought the secret of eternal youth, yet there's never been a pill, potion or vitamin capable of unequivocally extending the lifespan of a mammal. If Beryl Buck's mice end up living long after they ought to have died, it won't be just another news story. It will be the scientific find of the decade.

It will also firmly cement the belief that a "cure" for human ageing really is just around the corner. People's expectations on this front have been steadily growing for years, pumped up by the excitement that greets every laboratory invertebrate that defies death for a few weeks and every attempt to trace the genetic basis of long life in humans. And it's not just headline writers who've been getting dizzyingly optimistic about the prospects for staying young for longer.

"We now know ageing is neither inevitable nor necessary"—it is malleable, said Tom Kirkwood, professor of gerontology at the University of Newcastle, delivering the prestigious Reith Lectures for the BBC this year. Sea anemones and freshwater hydra show no signs of ageing. Several species of fish and giant tortoise live longer than us. If a reptile with a shell can live for 177 years, why shouldn't we?

Why indeed, says top-flight evolutionary biologist Michael Rose. Just as racehorse owners selectively breed animals for extra speed, so Rose has spent much of the past decade selectively breeding fruit flies for extra longevity in his lab at the University of California in Los Angeles. He now has prize flies that, thanks to their genes, live for 130 days instead of the usual 40. In fact, according to Rose, even immortality is achievable—and not just for flies. "I believe there are already immortal people," he told a newspaper earlier this year, meaning that there are already people around who could potentially live forever if they could avoid accidents and infections.

The new optimism reaches its high-water mark in the lab of another outspoken "longevity pioneer". Steve Austad of the University of Idaho is so convinced that somebody living today will still be alive and active come 2150 he's even placed money on it. Austad's descendants will pick up the winnings if he is right. It's the sort of stunt that plays well with the greying baby boomers who now run the world. "Look at the average age of the people in Congress and at the massive increase in

federal funding for this kind of work," says Simon Melov, the Buck Institute scientist who's running the mouse longevity experiments.

Part of that federal funding is even now set to launch the first human trial of a method for slowing the ageing process. Later this year, at three separate trial centres, human volunteers will begin trying to extend their lifespans, not by popping high-tech pills but by going hungry. The move is inspired not by some cranky theory but by the proven knowledge that rats and mice given only two-thirds of what they'd normally eat live up to 50 per cent longer. It's an effect scientists have known about for 65 years, but the new experiments will be the first serious attempt to see if people who burn fewer calories also age more slowly.

In fact, they'll be more than that. Until now, only specific illnesses such as cancer and heart disease have been deemed the proper targets of clinical trials. In splashing out $2.5 million on trials that view growing old as a treatable condition, the US government is signalling a change of attitude. In their own different ways, Beryl Buck's mice and those volunteering to go hungry in the name of longevity are setting a precedent that could widen the scope of medical science forever.

But can money and science really roll back the tide of human ageing? New Scientist looked behind the upbeat talk for the real story. We spoke to a wide range of experts, scoured the scientific literature and looked at the small print surrounding the spectacularly long-lived flies, worms and mice that have been making headlines in recent years.

The good news is that scientists clearly are making progress in understanding the molecular causes of ageing. The bad news (at least for those hoping for 60-plus years of retirement) is that few experts seriously believe that the lifespan increases seen in lab animals mean humans will be living even to 120—let alone 200—by the end of the century.

More worryingly, the scientific credibility that's been lent to claims about slowing down human ageing now seems to be doing tangible harm. In recent years, thousands of private doctors, clinics and Internet sites have set up shop offering a vast range of "anti-ageing" remedies, from herbal extracts and vitamins to powerful pharmaceuticals such as deprenyl and even antidepressants. Many trade on the hype surrounding the fly, worm and mouse experiments. And all exploit the current climate of optimism to market products of unproven value and safety. "We need to make sure that mainstream scientists no longer feed the quackery," says Jay Olshansky, an expert on ageing at the University of Chicago.

Of particular concern to many scientists is the use of human growth hormone as a rejuvenation therapy. The body can tolerate only minuscule amounts of this hormone, says Zvi Laron of Tel Aviv University, who helped pioneer the treatment of children deficient in the hormone. "We have no evidence showing what a safe dose is and what it does in adults."

What follows is our analysis of some of the half-truths, myths and simplifications about the science of ageing that have made us such willing believers.

Six myths about ageing

THANKS TO MODERN MEDICINE AND SCIENTIFIC ADVANCES, ADULTS TODAY CAN EXPECT TO LIVE INTO THEIR 70S OR 80S WHEREAS OUR ANCESTORS MOSTLY DIED IN EARLY MIDDLE AGE

A surprisingly durable myth, this one. Plenty of people in the 18th and 19th centuries lived a full three score years and ten—visit any old graveyard to see the evidence. What has nearly doubled in the past century is average life expectancy at birth. In countries like the US and Britain it was around 45 years as late as 1900. Now it's nudging towards 80 years—an impressive hike. Yet most of that gain came not from making adults live longer but from preventing babies from dying.

A century ago in the US, for example, around 15 per cent of babies died before their first birthday—think how that skews the average lifespan of a population. In truth, there never were any great waves of forty-somethings dropping dead, either before or during the Industrial Revolution.

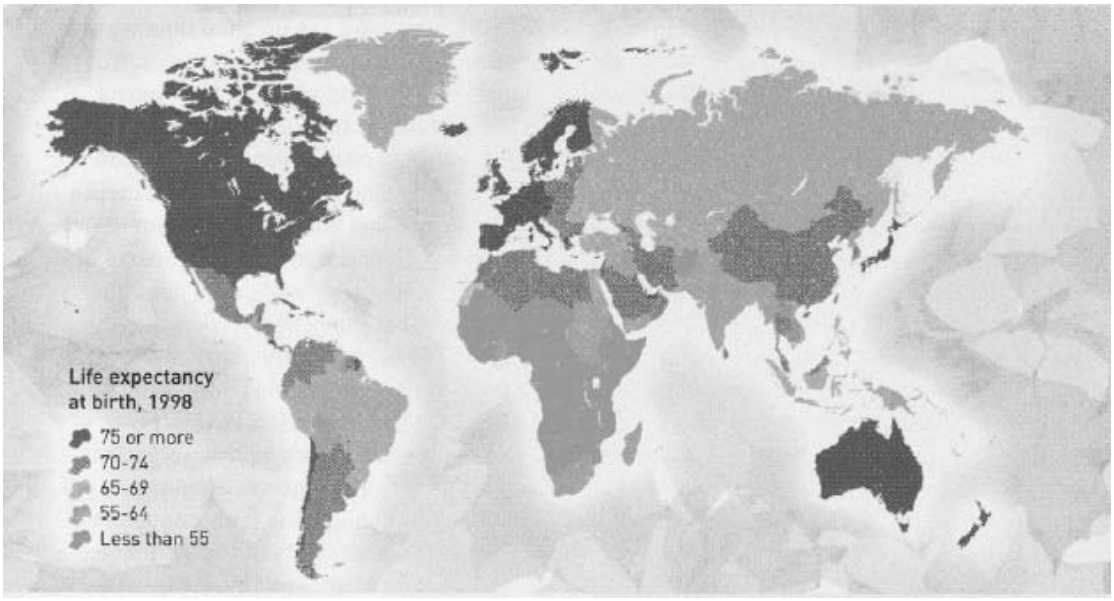
We've also overestimated the role of medicine in improving life expectancy. Vaccines and antibiotics did have an important part to play. But better hygiene, living conditions and diet did most of the work. The number of children dying from TB in Britain, for example, had already plummeted from its 19th-century high by the time effective antibiotics became available in the 1940s.

GIVEN THE HEALTH IMPROVEMENTS AND LONGEVITY GAINS OF THE 20TH CENTURY, PEOPLE COULD SOON LIVE ROUTINELY TO 120

Not as things stand. The big gains of the past century largely came from adding whole decades of life to infants who would otherwise have died—only a small proportion of the longevity leap came from tackling major killers of adults such as stroke and heart disease.

With very few infants and youngsters now dying in developed countries, the easiest source of extra human longevity has all but dried up and increases in life expectancy are slowing to a crawl. Even if every remaining death before 50 could be prevented in industrialised nations, it would add just 3.5 years to our life expectancy, says Olshansky.

Big gains in future can only come from tacking extra years on to the lives of the elderly—and that will require extraordinary medical breakthroughs. Longevity enthusiasts say we will soon be living to 120, but according to death rate statistics, medical science would have to eliminate every single common cause of human death just to reach a life expectancy of 100.



SCIENTISTS CAN MAKE WORMS AND FLIES LIVE MUCH LONGER THAN NORMAL, SO SOME SORT OF TREATMENT FOR SLOWING DOWN AGEING IN PEOPLE IS SURELY INEVITABLE

Far from it. Scientists might bill such creatures as "models" for understanding human biology but the differences are not exactly negligible. Nematode worms, remember, are sub-millimetre creatures built from only around a thousand cells, none of which is destined to divide. What's more, as far as anyone can tell, neither they nor their fruit fly lab-mates get diabetes or cancer or Alzheimer's disease in old age (and not having any bones, osteoporosis isn't much of a problem either).

So why have they become the mainstays of the science of ageing? Because their short lifespans make the experiments so much easier and faster. And this is the big flaw in research into longevity—much of it is based on lab creatures that lack it. Fruit flies usually live 40 days, worms just 20. Their baseline ability to resist ageing is a thousandfold worse than ours, so it's not surprising that it's so easy to boost it by tampering with their genes.

In addition, the worm's peculiar biology means that it has a naturally elastic lifespan and a vast reserve of hidden resistance to ageing. When food is scarce, nematodes go into a special state of hibernation. They stop feeding, developing and moving, and grow a thick protective skin. They also age far more slowly, lasting up to 70 days instead of the usual 20. And it's this reserve of hardiness that makes the worm's lifespan so easy to double or triple artificially.

You can make a worm live up to 60 per cent longer by altering any one of a certain family of genes known as "clock". But the mutants grow up, breathe, swim, feed and defecate more slowly and are far less fertile. "Live slow, die old" seems to be the trade-off these mutants make. Would anyone want to live to 120 if it meant going through puberty in their mid-20s and never playing sport?

What is clear is that "long life" mutations in lab mice—model organisms that at least have backbones—are rarer and nowhere near as dramatic as those seen in flies or worms. The mouse longevity record is held by a team that altered a gene for a hormone receptor called IGF-1. In mice, mutations in this gene boost lifespan by a respectable 80 per cent. In people, on the other hand, they lead to diabetes and a shorter lifespan.

WE COULD DRAMATICALLY EXTEND OUR LIFESPAN SIMPLY BY TAKING PROTECTIVE VITAMINS AND IMPROVING THE BODY'S DEFENCES AGAINST HARMFUL FREE RADICALS

Not wrong—but very optimistic. Our bodies produce free radicals all the time as cells convert oxygen and food into chemical energy. Free radicals can damage DNA and cell membranes in ways that might lead to ageing. Virtually all organisms have natural antioxidants and enzymes to stop this happening. Supplement these with antioxidant vitamins or drugs that mimic the enzymes and you will slow down ageing. This is the theory that underpins much of today's multibillion-dollar trade in vitamins and anti-ageing supplements.

The catch is that no matter how hard you try, you'll never eliminate all the free radicals. Even if you could, it might be harmful—our bodies need a certain number of free radicals to maintain their immune defences. Besides, the body's inbuilt defences against free radicals may be so good they're hard to improve on. Catalytic scavengers like EUK-8 and EUK-134 might help boost the weak defences of short-lived worms, but do nothing in people. Indeed, according to Stephen Helfand of the University of Connecticut, unpublished tests show that not even fruit flies respond to the drugs.

And there are other signs that boosting defences against free radicals is not the key to eternal life. Two of the most important enzyme defenders are superoxide dismutase and catalase. Flies engineered to make more of these enzymes live at most 10 per cent longer and some even have shortened lives. When the same mutation pops up in human superoxide dismutase it leads not to a longer life but to the nerve disease amyotrophic lateral sclerosis.

SEMI-STARVED RATS AND MICE LIVE UP TO 50 PER CENT LONGER, SO WE HUMANS SHOULD BE ABLE TO LIVE TO AROUND 120 SIMPLY BY COUNTING THE CALORIES

Unlikely, but virtually impossible to prove or refute with hard evidence. The idea that if you eat less you'll produce fewer damaging free radicals (and hence age more slowly) has an alluring simplicity—and no basis in fact. Athletes burn calories at a very rapid rate but there's no evidence this leads to premature ageing or a shorter life. True, lean people are more likely to outlive their fuller-figured brethren, but only because they're more likely to exercise and be physically fit.

So why does the tactic work so well in animals? One likely factor is that many strains of lab mice are genetically uniform and highly susceptible to lethal cancers later in life. Rationing their food seems to delay or prevent these cancers and hence extends their lifespan. But humans are not genetically uniform, and in old age we're more likely to die from cardiovascular diseases than cancer.

Our bigger bodies are also likely to be less responsive to metabolic emergencies. When calories are in short supply, small mammals such as mice often slump into an energy-conserving state akin to hibernation—movement stops, body temperature plummets. This seems crucial to the mice living longer. Warming the animal house up often causes the cancers to return and lifespan to

shrink back to normal. Human bodies display nothing like the fickle temperature range of a small mammal.

Another possibility is that caloric restriction can make people live longer, but only if the calories are cut to abnormally low levels. That could be so if caloric restriction works not by reducing the number of free radicals but by triggering a fundamental change in body chemistry—a change that boosts defences against all sorts of harmful agents, including free radicals. But scientists have no idea whether such a trigger exists.

It's 13 years since teams in the US began feeding macaque monkeys severely restricted rations and comparing them with control animals. Now in their 20s, the monkeys are said to be in rude health—less prone to diabetes and cancer, less cholesterol in the blood. But since macaques have, in captivity, an average life expectancy of 27 years and a maximum lifespan of around 40 years, it will be a decade before we know for sure whether they're cheating old age—but genetic tests on their muscles suggest they're ageing at the normal rate.

What's more, a macaque is not a person. That's why teams in the US are now gearing up to carry out the first long-term trials of caloric restriction in human volunteers. The initial aim is simply to see how people respond—in terms of behaviour as well as body chemistry—to eating so much less than their bodies really want.

But even if caloric restriction did work, would people stick to their diets? People who try it often end up living mainly on watery vegetables and vitamin pills, with bananas a rare luxury. And an informal survey by the US-based Caloric Restriction Society found as many as 40 per cent of those on a severely restricted diet complaining they lacked energy. One dieter complained of "especially severe sensitivity to cold" in his hands and feet. A second reported "haemorrhoid discomfort, rectal bleeding and easily damaged skin"—"just brushing up against something slices my skin open".

Some scientists are already talking about designing a drug that can somehow fool the body into thinking it's being semi-starved of calories even when it isn't. The problem with that idea is that we still don't know for sure why caloric restriction works. What's more, there's a very real possibility that giving your body a drug that makes it think it's being semi-starved (when it isn't) will simply make it hanker after extra helpings it doesn't need. And the result of that would be a fatter, shorter life instead of a longer, thinner one.

GROWTH HORMONE SUPPLEMENTS CAN HELP FORESTALL AGEING AND KEEP OUR BODIES YOUNGER. THE HORMONE IS ALREADY SOLD ON THE INTERNET AS AN ANTI-AGEING TREATMENT

The levels of some important hormones, including growth hormone, do wane as we grow older, so it's tempting to suggest that supplementing them might slow down the ageing process. But if the latest research is anything to go by, it may actually shorten your lifespan.

Ordinarily human growth hormone is produced by the pea-sized pituitary gland at the base of the brain. But it can also be manufactured in bacteria and injected. For decades such jabs were prescribed only for children with serious hormone deficiencies. Then in 1990 scientists gave injections to a dozen elderly men who over several weeks seemed to lose flab and regain hard muscle, taut skin and higher energy levels. Thus was born the idea that growth hormone jabs can help you defy ageing.

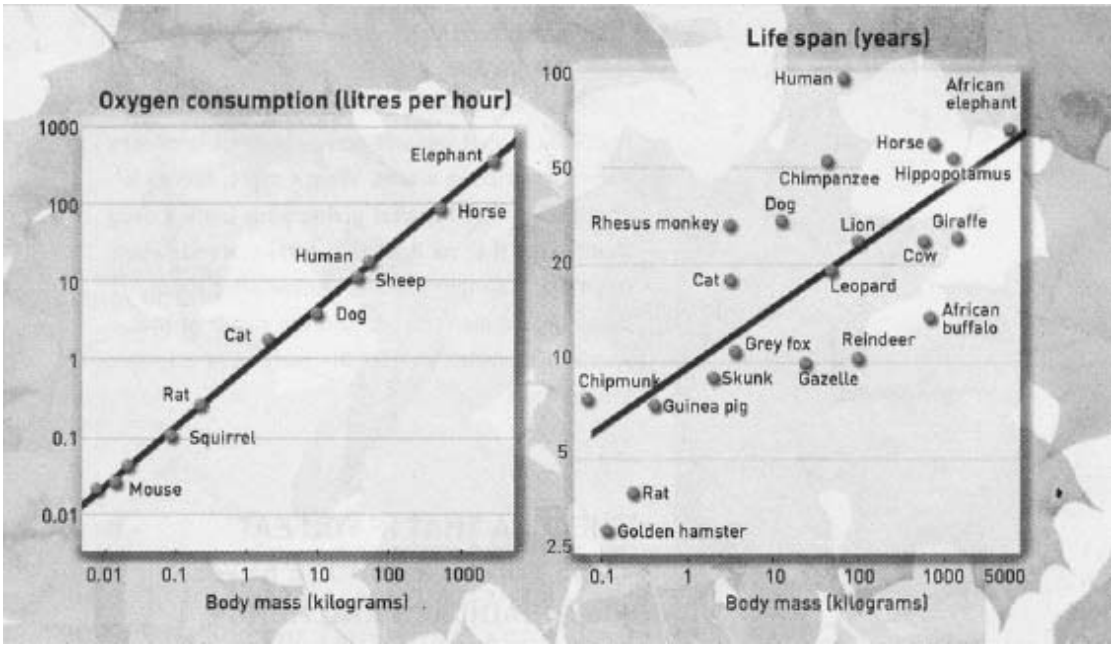
Today business is booming for the nine separate companies that make human growth hormone worldwide, and tens of thousands of Americans are reported to be enthusiastic users. Incredibly, though, scientists still can't say whether the hormone has the power to rejuvenate ageing bodies. The 1990 research was merely a small pilot study. Only now are teams in the US giving growth hormone—or drugs designed to mimic it—to large groups of young and old adults. The results won't be clear for years.

The same, unfortunately, can't be said for the dangers. Doctors have long issued warnings about the risks, and now the first reports are trickling into the medical journals of serious side-effects,

including voracious cancers among body builders who use growth hormone to bulk up their muscles.

A further blow comes from people who are naturally deficient in the hormone. For years, doctors believed such people age fast and die young. Not so. Laron has been tracking groups of such patients for decades and his work shows that while most do go grey and wrinkly early in life, those who exercise and eat healthily also go on to have normal lifespans.

In fact, far from making people live longer, Laron suspects that growth hormone shortens lifespans. Mice deficient in the hormone live up to 50 per cent longer, and so do fruit flies with mutations that prevent them from responding to the invertebrate version of the hormone. There's even evidence to suggest that with all other things being equal, shorter people, who have less growth hormone, live longer than tall people. What growth hormone offers may not be longevity at all but a tough choice between looking good today and living longer tomorrow.



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And now for the good news...

Don't despair. True, we know of no pill or injection that can slow down ageing in people. True, the best options for the future – free-radical scavengers and stringent dieting – seem unlikely to fulfil the high expectations being heaped upon them. But even though the prospects are poor for extending human lifespans well into a second century, we can still increase our odds of living up to that limit. That's because you, not your genes, are in the driving seat when it comes to setting the probabilities for your own natural lifespan.

Earlier this month, that view seemed to take a battering when a US team reported the discovery of a DNA signature on chromosome 4 that's more common in centenarians and other long-lived members of their families (*New Scientist*, 1 September, p 5). But whatever this genetic signature means, it's hardly crucial: about half the centenarians studied didn't carry it. In the population as a whole, genes determine no more than about 25 per cent of any longevity difference between two people. Someone who dies at 100 as opposed to 80 can, on average thank their lifestyle for 15 of the extra years and their genes for just 5.

But if lifestyle is so important, what lifestyle is best? Okinawa, a chain of islands stretching from Japan to Taiwan, holds some vital clues. Its 1.3 million inhabitants have the longest life expectancy on the planet and include no fewer than 400 centenarians – nearly four times the percentage found in Western countries.

In Okinawa, people still get old and grey. They're just better at keeping all the usual life-threatening symptoms of old age at bay. Women have fewer hip fractures. Heart problems and strokes come later or not at all. Fewer people succumb to hormone-linked cancers such as breast, ovarian and prostate, while the rate of colon cancer is just half that found in the US or Britain.

Since Okinawans who migrate to the West don't keep their long life expectancy, genes cannot be the crucial factor. So what's special about the lifestyle? Okinawans do not drink or smoke much and they eat little meat: three-quarters of their food comes from plants, with fruit, vegetables and fibre crossing their palates more often than fat or refined sugars. On top of that, the islanders practise a cultural habit called "hara hachi bu", which involves downing chopsticks at the first hint of fullness.

There's more to long life than just a healthy diet, though, insist the authors of the Okinawa Centenarian Study, a 25-year-old research programme funded by the Japanese government. Dancing, walking, gardening and gentle martial arts such as t'ai chi are all popular among the middle aged and elderly. And instead of turning to alcohol or Prozac in times of stress, Okinawans meditate or rely on their families.

Proving such factors are important to longevity is not going to be easy. But even in the West, studies suggest that optimistic people tend to outlive pessimists, and religious types outlive atheists. And of course the impact of diet is also evident in the West, in the longer lives of those who eat the Mediterranean way.

So let's say we all adopt the right lifestyle. Can anti-ageing drugs help us live even longer? It's possible, but scientists may have to change their approach. No one has found a central clock that dictates the rate of ageing in all tissues. For a time, telomeres – tiny bits of DNA that protect the ends of our chromosomes – looked like just such a clock, since they shrink bit by bit as cells divide. But the evidence to date suggests that different tissues wear out at different rates and for different reasons. As Richard Weindruch of the University of Wisconsin in Madison puts it: "The odds of finding one particular nutrient or drug to broadly retard ageing in all organs are not as good as the prospects of finding interventions that work on individual organs."

Weindruch and his team believe they've found the tool they need to develop such targeted interventions. Until now, scientists have had no way of knowing whether an experimental drug might slow the ageing of, say, bone or muscle cells, because they've had no way to measure the age of a single cell or tissue.

That's where genetics can help. As cells and tissues grow old, strange things happen to the thousands of genes that make them tick. Some genes, active for decades, stop giving out instructions and fall silent; others that have lain dormant since birth suddenly spring to life. This complex ebb and flow of gene activity is the most fundamental process of ageing – it is how we grow old deep inside our cells. And now scientists can track the process using gene chips, slivers of glass that can measure the activities of staggering numbers of genes.

In one study, Weindruch's team looked at more than 6000 genes in muscle cells of 5-month old and 30-month old mice. The activities of 58 genes more than doubled in the elderly mice, while another 55 genes were half as active. Since then the team has used gene chips to track changes in ageing animal brains and even in human muscles. The approach is also boosting the team's efforts to find drugs and nutrients to slow down ageing in lab mice. Previously, the researchers had to wait for the animals to die so they could measure their lifespan. "Now," says Weindruch, "we have a tool to measure the ageing process on an organ specific basis."

That will help enormously in testing the value of anti-ageing potions already being traded on the internet. Not long ago, Weindruch's team fed several such compounds, including vitamin E and co-enzyme Q, to mice and found little effect on lifespan. That could be because the substances don't work, but it could also mean that they benefit only certain tissues that aren't usually the first to fail in mice. Weindruch and his colleagues are now using gene chips to discover the answer.

It may seem like a small, technical advance, but this ability to finger print the ageing process at the level of genes could soon transform the hunt for combinations of anti-ageing compounds. In the long run, it may even help to change the very way we view the ageing process. Instead of imagining a single line running from birth to death, we may have to start thinking of parallel tracks,

one for each major tissue and organ in the body, with our lifespan determined by the length of the shortest track. The question, “How old are you?” will remain simple. The answer much less so.

Further reading: *The Quest for immortality* by Jay Olshansky and Bruce Carnes (W. W. Norton, 2001)

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