BOOKS & ARTS

Secrets of a long life

Two books on ageing understate the challenges of prolonging a healthy lifespan, finds **Caleb Finch**.

We are poised on the verge of being able to control ageing, according to two books. In *The Youth Pill* and *Long for This World*, science writers David Stipp and Jonathan Weiner each explain the latest findings in longevity research and in the commercial development of drugs to modulate or prevent ageing. Both books highlight the shift from treating diseases of the elderly towards the comprehensive control of ageing itself. Weiner weaves a more writerly narrative; Stipp examines the scientific advances in more detail.

The ageing process is clearly plastic. Human lifespans have more than doubled in the developed world since 1800, thanks to improved public health, hygiene and medicine. Today, centenarians comprise the fastest growing age group. The successful control of ageing in laboratory animals has kindled expectations for interventions and drugs that might prolong human lives.

But there is a dark side to living for a long time, as Stipp touches on in *The Youth Pill*. Dementia increases exponentially after the age of 65 and affects about 50% of those aged 100 and older. The US Alzheimer's Association predicts that dementia cases will triple by 2050 to affect 13.5 million people aged 65 and over in the United States alone. Pensions, social and medical support are underfunded: there are only around 7,000 geriatricians for the 35 million US citizens aged over 65. Escalating health-care costs for the elderly threaten to swamp national budgets. Robert Butler's *The Longevity Revolution* (PublicAffairs, 2008) considers these issues more closely.

The Youth Pill: Scientists at the Brink of an Anti-Aging Revolution
by David Stipp
Current: 2010. 320 pp. $26.95

Long for this World: The Strange Science of Immortality
by Jonathan Weiner
Ecco: 2010. 320 pp. $27.99

Stipp and Weiner both document several widely cited lab studies of animal ageing models, with Stipp digging deeper into the research. Genetic manipulations of metabolic pathways have increased the lifespans of mice by 50%, and made that of nematodes ten times longer. Dietary restriction also slows ageing, and can extend the lifespans of lab rats by up to 40%. Decades of research on dietary restriction has led to testable hypotheses on links between the oxidative effects of metabolism, tissue damage and various diseases. But ageing studies in primates have been inconclusive. The dietary effects on ageing are best described in Greg Critser's *Eternity Soup* (Harmony, 2010; see also *Nature* **464**, 491–492; 2010), named after the recipe for long life conceived in Renaissance Italy by Luigi Cornaro — a story that both Stipp and Weiner also relate.

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Centenarians now constitute the fastest-growing age group owing to advances in health care.

Efforts are under way to mimic dietary restriction in humans using a 'youth pill'. These include the development of drugs that block the metabolic pathways of sirtuin enzymes and mTOR protein signalling. Both pathways are involved in many ageing processes, normal and diseased. Resveratrol — a polyphenol from red grape skins that targets sirtuins — prolongs the lifespans and increases the motor coordination of mice made obese by a high-calorie diet. These findings have triggered a burst of commercial development.

The pharmaceutical industry is interested in the profitability of anti-ageing remedies and is willing to invest big sums; GlaxoSmithKline paid more than US$720 million to acquire the specialist sirtuin firm Sirtris in 2008, for example. Both Stipp and Weiner rightly warn that, as for any drug, longevity boosters must follow a long and tortuous path of tests to gain approval. Stipp points out that even though many biotech start-ups have tried, few have developed effective age-modulating drugs. Even after approval, drugs that target multiple systems may reveal new side-effects in ageing groups who have diverse conditions.

Faith that such drugs will eventually pass all the hurdles may be premature given the many complexities that underlie the animal studies. Environmental variation may overlap with drug effects. Neither book discusses the Interventions Testing Program of the US National Institute of Aging, which trials anti-ageing drugs at three separate sites using the same mouse stock. The increase of lifespan in mice fed with rapamycin, a drug that affects mTOR signalling, differed up to two-fold between these sites. Local factors also affect lifespan in other animal studies. For example, researchers studying mutant dwarf mice in the 1970s observed their short, six-month lifespans and accelerated ageing. Improved husbandry, including the elimination of infections once endemic in rodent colonies, now enables dwarf mice to live ten times longer than normal mice, with slowed ageing.

The dwarf mutation and some others that alter metabolism also affect immune responses and wound healing, as do caloric restriction and resveratrol. This raises the question of whether longevity drugs that weaken immune defences would work in our dirty, germy world. Who would want extra decades if it meant living in a bubble? The unusual genetics of inbred lab rodents, selected over decades for rapid growth and large litters, may also skew results, as Stipp notes briefly. Wild-caught mice are smaller and reach maturity later. The effects of diet restriction on lifespan in wild mice

were modest relative to most lab-bred rodent studies. For these and other reasons, the extension of rodent findings to humans is fraught with uncertainty.

Although recognizing some biogerontology pioneers, Stipp and Weiner give the impression that the field has only gained respect recently, with the identification of gene mutations that extend lifespans in model organisms. The advent of recombinant genetics accelerated progress in ageing research in the 1980s, but this phase built on several decades of biochemical, cellular and physiological studies. This has parallels with the field of developmental biology: the century of classical embryology that defined the cell lineages in differentiation enabled the recent understanding of genes that regulate development. However, neither book addresses the deep links between development and ageing. It is the genetic regulation of differentiation that determines which cells and molecules are replaced in adults; for example, the elastin in our arteries ages progressively because it is not replaced.

If humans could retain the mortality rates of young adults, our survival curves would resemble radioactive decay, with median lifespans of more than 500 years. The general exponential increase of mortality is driven by numerous morbidities, but particularly by arterial disease and cancer. The utopian goal of arresting ageing is propounded by British gerontologist Aubrey de Grey, who plans to engineer negligible senescence through a multi-pronged attack on each molecular and cellular cause of ageing. Weiner's book is almost a paean to de Grey; he is treated with greater balance by Stipp.

De Grey's goal of negligible senescence extends my use of this terminology in 1990 to describe rockfish, turtles and other long-lived species that showed no decline in reproduction, no age-related pathology and no mortality acceleration (updated in C. E. Finch *Gerontol.* **55**, 307–313; 2009). Another such species is the naked mole-rat, which lives for up to 30 years while maintaining reproduction but without incurring tumours or other age-related disease. Nonetheless, its cells exhibit considerable oxidative damage. Such examples challenge the evolutionary theory that senescence is inevitable or a simple sequel to oxidative stress.

In both Stipp and Weiner's accounts I had hoped for more on the comparative and evolutionary approaches to ageing, which promise to identify systems of genes that regulate many such processes, by analogy with developmental gene regulation. Also missing is a discussion of how global climate change will affect future life expectancy. Both books include a few misleading statements: brain shrinkage during normal ageing after the age of 50 is "like a bowl of Jell-O left out in the hot sun", writes Stipp; Weiner holds that fibroblasts get "old and tired". In fact, extreme brain shrinkage after 50 occurs mainly from Alzheimer's disease, and senescent fibroblasts can live for years if growth media are refreshed.

"The conclusion that we are on the threshold of controlling ageing is premature."

The conclusion of both these useful summaries of longevity research — that we are on the threshold of controlling ageing — is premature. We have much to learn about the ageing process, and developing drugs to combat it is an increasingly complex challenge. We cannot simply extrapolate into the future from the remarkable lengthening of lifespans during the past two centuries. ■

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Our conflicted relationship with animals

Some We Love, Some We Hate, Some We Eat: Why It's So Hard to Think Straight About Animals
by Hal Herzog
HarperCollins: 2010. 336 pp. $25.99

Attitudes to animals are strongly held and hotly contested. In *Some We Love, Some We Hate, Some We Eat*, psychologist Hal Herzog opens up the new field of anthrozoology, the study of how humans interact with other animals. Showing wide sympathy with all the actors in this drama, he draws attention to the inconsistency of our views.

Herzog strives for what philosopher Strachan Donnelley called "the troubled middle". He argues that moral absolutes are not readily available in a complex world — one that exists in shades of grey, rather than the black and white of animal activists and their opponents. Those who adopt the centre ground are not fence-sitters, Herzog says. Instead, "moral quagmires are inevitable in a species with a huge brain and a big heart".

Cats are a good example of our conflicted attitudes. They share our homes, and

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Cat owners favour their pet's freedom over its prey.

experiments on cats are a prime focus of animal-rights extremists. Yet these cute carnivores cause countless bird and rodent deaths each year, even when well fed. Pet cats in the United States consume 4.5 million kilograms of animal flesh in cat food every day. In one study, three-quarters of a group of cat owners who were informed about their pets' destruction of songbirds said that they would still let their cats play outdoors.

Herzog has a clear eye for the essence of a scientific study, but he leavens his narrative with illuminating personal stories and self-deprecating humour. He offers a vivid account of his job in a chemical ecology lab, when he found himself unable to follow instructions to boil a mouse alive to collect samples from its skin. His accounts of cock fights in the mountains of North Carolina are full of wit and relevant detail, and he lets the breeders, gamblers and protestors speak for themselves. Herzog concludes that he would rather be raised as a fighting rooster than as a battery chicken headed for the cooking pot. He takes the same nuanced approach with vegan animal-rights activists, neither demeaning nor endorsing them.

Herzog's acknowledgement of complexity puts him in a good position to try to understand pet keeping. Could this unique human characteristic be adaptive, such that pets serve useful functions? Or are they parasites? Herzog concludes that there is no need to assume the myth of single causation. Pets can have many purposes: some adaptive, others less so.