BORROWED TIME

The Science of How and Why We Age

Sue Armstrong

BLOOMSBURY SIGMA
LONDON • OXFORD • NEW YORK • NEW DELHI • SYDNEY

CHAPTER ONE

What is ageing?

Biology is restless, never still. Our bodies are changing constantly in response to signals from within, and from the outside world. 'As a result of this unremitting change that begins at conception,' says biologist Richard Walker, 'ageing, the seed of death, is planted within each of us on the day we are given life.' In his book, *Why We Age: Insight into the Cause of Growing Old*, Walker describes growing up in America in the 1950s and '60s, an enthusiastic hippy in pursuit of youthful ideals, freedom and fun. But unlike most of his peers, he harboured a deep fear, even resentment of old age. 'One of the greatest wonders of youth,' he writes, 'is that there are really no limits to the things that your mind thinks you can achieve. So one evening while riding in my classic 1954 MG model TF with the top down and flush with the bloom of youth in body and spirit, I decided to find the cure for ageing.'

But the question then, as now, was: at what stage do the continuous changes in our bodies stop being constructive – driving tissues and organs towards maturity and optimal function and organisms towards harmony with their environment – and instead become destructive? In other words, what is ageing?

'Ageing is the universal, progressive and intrinsic accumulation of deleterious changes,' says one gerontologist. 'Ageing is the gradual failure of health maintenance systems in our bodies,' says another. 'Ageing is a disease – or a disease super-syndrome, if you like,' says another. 'I think damage over time is what ageing really is.' 'It's dying from the inside.'

Without consensus or a clear definition of when ageing begins, how it happens and why, scientists studying the process are left shooting at moving targets in the mist, trying to deduce the rules of a game that is being played out before their eyes. It is not surprising, therefore, that dealing with the ravages of age has focused on addressing the individual diseases – conditions such as cancer, heart failure and dementia – that are clearly and unequivocally pathological. Almost nowhere in medical training, let alone in the popular mind, is there appreciation of the fact that ageing itself might be the problem – that these diseases are the symptoms, the end game – and that just because ageing is a natural process that happens to us all inexorably if we avoid early death, it doesn't mean that it is either healthy or intractable.

The Greek philosopher and scientist Aristotle, alive in the fourth century BC, believed ageing was the result of gradual cooling of internal organs – in other words, the quenching of some internal flame. The ancient Chinese believed it was the result of imbalance or loss of a vital essence stored in the kidneys that sustains all bodily functions. This idea underpins traditional Chinese medicine today, which prescribes acupuncture, special foods and herbal concoctions to restore the body's balance between yin and yang – its passive and active life forces – to maintain health and youth. So, too, all kinds of present-day practices, such as yoga, meditation, massage with aromatic oils and the taking of herbal infusions, have their roots in ancient beliefs and customs from India about how to ward off time's depredations.

The first modern theory of ageing was proposed in the late nineteenth century by August Weismann, a German biologist considered by some to be one of the most important evolutionary thinkers of his time. In a nutshell, Weismann suggested that our biology could not withstand indefinitely the constant barrage of insults and injuries of daily living, and that Nature's solution was to replace

worn-out bodies with new, undamaged ones. He came up with the idea that the inheritance of traits is passed on in 'immortal' germ cells (sperm and ova) and that the cells of the body, known as somatic cells, take the brunt of life's insults and have a naturally limited lifespan; once the body has matured and reproduced, it begins to decline.

Weismann originally believed ageing and death to be programmed; that evolutionary forces had selected for a death mechanism that would remove damaged individuals once they had fulfilled their primary purpose of passing on the gift of life, in order to prevent competition for space and resources with succeeding generations. 'Worn-out individuals are not only valueless to the species,' he wrote in 1889, 'but they are even harmful, for they take the place of those that are sound.' Though the theory of purposeful, programmed death will forever be associated with his name, in fact Weismann began to have doubts as he himself grew older. He modified his views, suggesting that old individuals were not the burdensome nuisance he had originally believed, that their effect on the species was neutral; ageing and death may not, after all, be programmed, but the result of progressively worn-out bodies simply running out of steam at their own pace.

Evolutionary ideas dominated the field in its early days, and continue to provide the framework for much of what goes on in geroscience today. In 1952, the British biologist Peter Medawar, who won a Nobel Prize in 1960 for his work on the immune system and transplant rejection, wrote a paper setting out his theories of why we deteriorate with age. Evolution occurs as a result of random mutations in the DNA of egg and sperm cells. Over eons of time, those mutations that confer benefit, increasing our fitness to reproduce, are the ones that survive in our species, while the ones that weaken us, increasing our chances of dying before we reach maturity, or too soon thereafter to have raised many offspring, will die out.

Genes, however, are not all expressed at the same stage in life and Medawar reasoned that it is possible for a mutation to occur that doesn't reveal its ill effects until late in life – possibly even beyond the childbearing years. The later in life a gene mutation is expressed, the weaker the ability of natural selection to eliminate it, and for this reason Medawar dubbed the post-reproductive period a 'genetic dustbin'. The harmful, late-acting mutations that have accumulated in this genetic dustbin are, suggested Medawar, the drivers of ageing. Dramatic examples of such harmful dustbin genes are the ones for Huntington's disease and familial Alzheimer's, both of which cause deadly degeneration of the brain that typically develops in later life.

Just five years after Medawar's paper, in 1957, the American evolutionary biologist George Williams came up with a deeper, more sophisticated version of this same theory. A single gene can have multiple effects in the body, depending on where and when it is expressed – a phenomenon known as pleiotropy. This multipurpose characteristic of genes helps explain why such a complex organism as ourselves can be produced by only about 20,000 genes – hardly more than the microscopic worm *Caenorhabditis elegans* (*C. elegans*) that is so popular as a model organism in biology labs.

Williams suggested that a gene mutation that has beneficial effects early in life might have harmful effects later in life, and this he termed 'antagonistic pleiotropy' – an ugly bit of biological jargon that cannot be avoided because it crops up all over the show in gerontology research. As in Medawar's 'mutation accumulation' theory, the harmful effects of the mutation would be hidden from the forces of natural selection because they don't compromise reproduction. Or, as Williams himself put it: 'natural selection will frequently maximize vigor in youth at the expense of vigor later on and thereby produce a declining

vigor (ageing) during adult life.' Unsurprisingly, some have dubbed this, more graphically, the 'pay later theory'.

Williams gave two graphic examples of his idea. One involves the calcium circulating in your blood. You need this to draw on freely when you're young, to build and remodel your skeleton and to mend broken bones quickly so that you're not crippled and vulnerable. This would have been essential to survival for our hunter-gatherer ancestors. However, if you get to be 65 or 70 – as you so rarely did in pre-modern times – all that calcium in your blood begins to settle in your vascular system and you get hardening of the arteries, a classic condition of old age. But that is of no consequence to the forces of evolution: you will have had your babies already and done your bit for the species.

The other example Williams liked to give featured testosterone, the sex hormone responsible for the growth of the prostate, the gland at the base of the penis that supplies fluid to protect and nourish the sperm. Genetic variants that encourage overproduction of this hormone may also stimulate overabundant growth of the prostate that, in younger men, may increase their sex drive and reproductive success, giving them an advantage in the natural selection stakes. But it frequently causes problems for older men – most commonly, difficulty with urinating because it puts pressure on the bladder and the tubes leading out of it, and prostate cancer as the errors build up in the continuously dividing cells.

Fast-forward 20 years to the late 1970s and Tom Kirkwood, a mathematician working in medical research on blood disorders, has been thinking about one of the mysteries of cell division seen in lab dishes – namely that they inevitably grow old and die after a certain period of time. His interest has been stimulated by a chance meeting at work with a molecular biologist, Robin Holliday, who sought his help with modelling how errors in copying the DNA between one generation of cells and the next might build up. Could

this be the key to ageing in us? Ageing was way outside his usual focus on blood, but Kirkwood remained fascinated. His reading around the subject in his spare time introduced him to the ideas of August Weismann, and as his thoughts crystallised, he developed a theory of ageing that built on Weismann's distinction between the immortal germ cells, sperm and eggs, and the mortal somatic cells of the body. He published his 'disposable soma theory of ageing' in 1977 in the journal *Nature*.

In a nutshell, the argument goes like this: for an organism living in the natural world with all its hazards, the most important consideration – the biological imperative, if you like – is that it survives long enough to reproduce and nurture its offspring to independence. Maintenance of the cells as they ceaselessly divide to ensure that they do so without error is energy intensive; in an environment where resources are limited or hard-won, it makes sense to invest most heavily in maintenance of the germ cells through which life is passed on, rather than in maintenance of the soma (the body), which is only required to last until it has successfully launched the next generation.

In short, making cells immortal is extremely costly biologically, and why bother with whole organisms if they are likely sooner or later to succumb to accident, disease or predation out there in the supremely indifferent world? Natural selection is concerned only with the survival of the species, not the individual. Hence, says Kirkwood, only our germ cells – the crucibles of life – are immortal, while our bodies are 'disposable'. They age gradually as a result of lack of investment in maintenance machinery.

I first met Tom Kirkwood in the 1990s when I was making a documentary on ageing for BBC radio. So, on a crisp

February morning in 2017, I set off by train from my Edinburgh home for his office in Newcastle to find out more about the disposable soma theory – how he came up with it and whether it has stood the test of time.

Kirkwood is a quiet man who holds your attention with an unblinking gaze behind wire-rimmed specs as he talks in a slow, thoughtful manner. He was born in South Africa, where his grandfather had been a low-paid worker in the gold mines east of Johannesburg and his father, who left school at age 14, was a self-made man. Kirkwood's parents met during World War II when his mother, who grew up in Rhodesia, volunteered as a nurse in a military hospital in Nairobi to which his father had been sent from the war front in Egypt suffering from malaria. Much influenced by his experiences during the war, Kirkwood senior became heavily involved in race relations issues back home in South Africa, and in resistance to the Nationalist government that came to power in 1947 and the following year introduced the policy of racial segregation known as *apartheid*. In 1955 he moved his family to England, where he was appointed the inaugural Professor of Race Relations at Oxford University.

'Oxford in the fifties was a lovely place,' says Kirkwood. 'We had a college house which had been a large, ramshackle Victorian vicarage. It was a household of six children, and it was always open. We had friends and colleagues of my father's visiting from all over the world, but he specialised in African studies so we had a lot of people coming through from Africa – people who later became the heads of the newly independent former Commonwealth states. So it was a household that was open and full of discussion and ideas.'

Though he took a degree in maths at Cambridge University, Kirkwood had always been interested in biology, an interest nurtured by long spells back in the

wild, open spaces of southern Africa as he grew up. It is not surprising, then, that ageing as a topic should have appealed to him, since mathematical and biological approaches are complementary disciplines in unravelling its deep mysteries. 'I can remember very vividly how I suddenly saw the implication of the work I'd been doing for the last couple of years [with Robin Holliday],' he said with a smile of reminiscence. 'It was February 1977, a cold winter's night and I was lying in the bath and musing on this, when suddenly I realised that, *of course*, the work had shown that you could avoid the propagation of errors if you invested enough energy in error suppression.'

Kirkwood had been musing, too, on August Weismann's ideas about the distinction between egg cells and body cells, and lying back in his bath that February night he suddenly realised how the two trains of thought fit together. 'It would be worth investing [in good-quality error suppression] in the germline. Indeed you'd *have to* do it in the germline … If you hadn't evolved to do that in the germline we wouldn't be here today,' he explained. 'But then for the rest of the cells of the body, perhaps this is just too expensive. The vast majority of animals in the wild die young – very few of them make it through to the kind of age when ageing is itself a problem – so all you need is enough maintenance to keep the body in decent shape [until it has reproduced].'

This was the seed of the 'disposable soma' concept. Excited, Kirkwood got out of the bath and scribbled his idea on a piece of paper lest he forget it while on duty travel to Sweden the next day. When he came back he worked on it, then wrote it up as a scientific paper proposing a new theory. 'I was so new to science and I hadn't had the benefit of a conventional scientific training,' he explained. 'So I wanted to run it by key people who wouldn't have hesitated to tell me that I was barking mad – or that it had all been

done before!' He ran the idea past Robin Holliday, past Leslie Orgel, a British chemist known for his theories on the origins of life, and past John Maynard Smith, whom Kirkwood considered 'the greatest evolutionary biologist of his day', with whom he had had some contact already.

'They all really liked the idea, so it was published in 1977, and it was quite interesting, the reaction to it,' he said. 'A couple of years later I was at my first international conference on ageing in the States. There was an American gerontologist who got a little drunk in the bar and he prodded me in the chest and said, "'Tom, your paper in *Nature*, we did that with my journal club* a few months ago with my students and we haven't laughed as much in years!" So I don't think the idea immediately took off …'

Kirkwood's theory begs an obvious question: if ageing and death are consequences of built-in obsolescence – a strategy of investing only enough in maintenance of body cells to ensure a good chance of launching the next generation – do long-lived species invest more in maintenance of their bodies than short-lived species? In 1977 such questions could not be tested. But technology has advanced at startling speed, so that today researchers can watch what is going on in single cells in real time. In 1999 one of Kirkwood's PhD students, Pankaj Kapahi (whom we'll meet again later in our story), set out to test the disposable soma theory for his doctoral thesis. He took skin samples from eight different mammal species with very diverse lifespans, grew their cells in lab dishes and threw bad things at them. The prediction was that the cells from long-lived species would be able to handle the bad stuff better than the short-lived species, and that's exactly what Kapahi saw.

* Journal clubs are groups of people who get together regularly and usually informally to critically evaluate interesting articles in the academic literature relevant to their discipline.

'The theory was beautifully confirmed,' smiles Kirkwood. 'Kapahi's work acted as a benchmark for a whole series of subsequent studies that have tested this theory in a variety of ways, and they have confirmed time and again that there is this fundamental property – that longevity is bought, effectively, by investing in better maintenance and repair.'

In 2004, scientists working on embryonic stem cells made a very interesting discovery that further endorsed the disposable soma theory. Embryonic stem cells can be programmed to become any type of specialised cell that is required in the body. The researchers found that these earliest precursors of all other cells are, like the germ cells, immortal: they too can proliferate indefinitely. But what most excited Kirkwood and the disposable soma people was the revelation that within days of an embryonic stem cell being programmed to produce a specialised body cell (a process known as *differentiation*), the whole suite of maintenance mechanisms is downgraded. These mechanisms include the DNA repair tools, and the antioxidant defences that protect our cells from the harmful by-products of metabolism (burning sugars to produce energy). 'For me this was an absolutely wonderful moment,' says Kirkwood, 'because in the original disposable soma paper, I had predicted that the energy-saving strategy that would reduce the investment in suppression of errors should occur at or around the time of differentiation of the soma from the germline.' A pause as he looks back over time, and then he chuckles. 'You know there are very few moments in science when you can say, "I told you so!"'

Kirkwood's theory suggests an answer to another intriguing question: since all animals are made up of the same cells, the same basic building blocks, why is there such huge variety in lifespans across species? The disposable

soma theory suggests that the degree of investment in maintaining the body of any creature, and thus its lifespan, is determined by its environment. If its chances of survival are short, versions of genes that promote swift maturity and reproduction will be favoured by natural selection over those that delay these vital life events. Thus mice, which are highly vulnerable to predators, typically live only a matter of months in the wild, whereas the equally tiny pipistrelle bat, which can evade predators with its aerial acrobatics, can live to around 16 years.

Although in this disputatious field of science it still has its critics, Kirkwood's 'disposable soma theory', which he has further refined over the years, provides a plausible explanation for *why* ageing occurs, and a framework for many of the ideas that have been developed since about *how* it happens. In 2013 a bunch of scientists working on diverse topics relevant to ageing decided to draw up a list of 'hallmarks of ageing' – characteristics of the elderly body that 'represent common denominators of ageing in different organisms, with special emphasis on mammalian ageing' – to help bring conceptual clarity to the field and to guide research. In so doing they were taking a leaf from the book of cancer research, which gained major momentum after a similar exercise in 2000 when two cancer scientists, frustrated by the scattergun approach of their field, drew up a list of six defining features (expanded to 10 in 2011) known as 'the hallmarks of cancer'.

In drawing up their hallmarks of ageing, the scientists, led by Carlos López-Otín of the University of Oviedo in Spain, set three essential criteria: that a characteristic should be manifest in normal ageing; that if it were aggravated under experimental conditions, it would accelerate the normal ageing process; and that if it were ameliorated under experimental conditions, the normal ageing process would be retarded and lifespan increased.

The nine characteristics that fit this bill are:

- **Instability of the genome.** This is a result of the accumulation of genetic damage throughout life, and can be caused by all manner of things intrinsic and extrinsic to the cells, such as errors in copying the DNA during division, activity of the toxic by-products of energy production within cells, or physical, chemical or biological threats from the outside.
- **Telomere attrition**. Progressive shortening of the telomeres, which are the protective caps on the ends of chromosomes often described as being like the little plastic tips on shoelaces. Every time a cell divides and its chromosomes are copied, a few bits are lopped off the ends, and the telomeres get shorter. When they get too short for the stability of the chromosome, the cell will stop dividing and its nature and function will change.
- **Epigenetic alterations**. Each cell contains a full complement of genes contained in our DNA, but the individual genes are only activated when and where they have a job to do. Otherwise they sit there in the DNA doing nothing. The action of the genes is orchestrated by chemical compounds and proteins that can attach to the DNA and switch genes on or off and modulate their activity. Together these chemical compounds and proteins comprise the 'epigenome' (meaning 'beyond the genome'), which throughout life accumulates defects that in turn affect the activity of the genes.
- **Loss of proteostasis**. Cells contain a vast abundance of proteins, which are the products of activated genes and which carry out almost all the tasks in our bodies. Proteostasis is the process by which the cell brings order to this potentially unruly mob of individual proteins, which are otherwise all focused on their own goals.
- **Deregulation of nutrient sensing**. Cells have evolved exquisite mechanisms for adjusting their

behaviour to make the most of the nutrients available for generating energy and providing raw materials for growth. These mechanisms rely on sensors that constantly relay signals about the body's nutrients status.

- **Mitochondrial dysfunction**. The mitochondria are the cells' batteries. They are organelles found in large numbers in all mammalian cells except the mature red blood cells, and their main task is to take in nutrients (sugars and fats) from the cell and break them down to produce energy.
- **Cellular senescence**. Cells that normally divide lose their ability to do so after a certain number of divisions, as measured by shortening telomeres on the ends of their chromosomes. They then enter a state of permanent arrest known as senescence. Besides shortened telomeres, other forces, such as irreparable damage to the DNA or epigenetic alterations, can also cause cells to senesce.
- **Stem-cell exhaustion**. Adult stem cells are undifferentiated cells kept in reserve for repair and maintenance of the body. They are found tucked away in most tissues and organs, and can be programmed to replace lost or damaged cells in the tissue in which they are found. Over the years, these reserves get run down.
- **Altered communication between the cells of the body**. This is a result primarily of chronic, low-grade inflammation of the tissues.

These hallmarks describe the common, universal characteristics of ageing – and they provide strong reference points for the various researchers as they roll up their sleeves and get on with the investigation. But what researchers following any of these paths share with their fellow researchers travelling different paths is the desire to know what kicks the whole thing off, or what and where are the master switches of the ageing process.

Musing about the origins of organic life, which had been his obsession, the brilliant British chemist Leslie Orgel called it 'chaotic intellectual territory'. Much the same could be said about ageing. But a combination of burning and sometimes brilliant brains and rapidly evolving technology is affording us some fascinating and important insights into what is happening deep within our bodies and beginning to make sense of the great mysteries of ageing and death.