

Power, Sex, Suicide

Mitochondria and the Meaning of Life

Part 7. Clock of Life: Why Mitochondria Kill us in the End

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About

Dr Nick Lane is a British biochemist and writer. He was awarded the first Provost's Venture Research Prize in the Department of Genetics, Evolution and Environment at **University College London**, where he is now a Reader in Evolutionary Biochemistry. Dr Lane's research deals with evolutionary biochemistry and bioenergetics, focusing on the origin of life and the evolution of complex cells. Dr Lane was a founding member of the UCL Consortium for Mitochondrial Research, and is leading the UCL Research Frontiers Origins of Life programme. He was awarded the 2011 BMC Research Award for Genetics, Genomics, Bioinformatics and Evolution, and the 2015 Biochemical Society Award for his sustained and diverse contribution to the molecular life sciences and the public understanding of science.



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The immortal elves in Tolkein's immortal epic are as mortal as the next man. They die in droves on the battlefield. What they don't do is age, or at least not much. Elrond, Lord of Rivendell in *The Lord of the Rings*, was thousands of years old, dwarfing even biblical lifespans. Tolkein described his face as "ageless, neither old nor young, though in it was written the memory of many things, both glad and sorrowful. His hair was dark as the shadows of twilight..."

Is this just the whimsy of an imaginative mind? Not necessarily. While ageing and the degenerative diseases it carries with it are the bane of the western world, they are not a universal currency throughout nature. Many giant trees, for example, live for thousands of years. Admittedly, trees are a long way removed from ourselves, and in any case much of the tree is just dead structural support. Better examples, far closer to home, are many birds. Parrots can live for over 100 years, the albatross for more than 150. Many gulls live for seven or eight decades and show few overt signs of ageing in a way that we can recognize. A famous pair of photographs depicts the Scottish zoologist George Dunnet with a fulmar petrel that he had captured and ringed in Orkney. The first photograph shows Professor Dunnet as a handsome young man with a handsome young bird in 1952. The second was taken in 1982, and shows Dunnet with the same ringed fulmar, which he fortuitously recaptured 30 years later, again in Orkney. Dunnet is by now betraying the ravages of age, but the bird has aged not a jot, at least to the naked eye. A third photograph, which I have never managed to see, apparently pictures Dunnet with the same fulmar in 1992, just a couple of years before the death, after protracted illness, of one of them. Rest in peace, Professor Dunnet.

Yes, I hear you say, but we too may live for 100 years or more; what is so special about

a bird that does the same? The answer is that birds live far longer than they 'ought' to on the basis of their metabolic rate. If we lived as long as a lowly pigeon, relative to our own metabolic rate, we'd live happily, without much illness, for perhaps a few hundred years. So why not? Why not indeed! Given the political will to overcome the ethical dilemmas, there may be no biological reason why not. Over six million years of evolution, since we split off from the apes, we have already extended our own maximum lifespan by five or six-fold, from 20 or 30 years to about 120 years. As depicted in the familiar evolutionary succession, from the stooped knuckle-dragging ape to the erect homo sapiens, we have grown in weight as well as stature, and have a lower metabolic rate. These changes were wrought by natural selection – tampering with the genes – which if we were to apply them to ourselves would be called genetic modification. But even if we lack the stomach to meddle with our genes in the interests of a vainglorious immortality, still the best way to counter the desperate degenerative diseases of old age, which debilitate an ever-growing proportion of the population, is by applying the lessons of evolution in an ethically acceptable way.

I say 'relative to metabolic rate'. Recall from Part 4 that in mammals and birds, body mass corresponds to metabolic rate: in general, the larger a species the slower its metabolic rate. For example, the cells of a rat have a metabolic rate that is seven times faster than our own. It's no coincidence that the rat also lives for a fraction of the time. The relationship between metabolic rate and lifespan can be perceived more directly in insects such as the fruit fly *Drosophila*. In this case, the metabolic rate depends on the ambient temperature, and roughly doubles for every 10°C rise in temperature; and with it, their lifespan falls from a month or more to less than a couple of weeks.

Among the warm-blooded mammals, which are relatively immune to the vicissitudes of weather, there is a broad correlation between body mass, metabolic rate, and lifespan – the larger the animal, the slower the metabolic rate, and again, the longer the life. A similar relationship holds true if we plot out the birds, but now, intriguingly, there is a gap (Figure 12). On average, if a bird and a mammal are paired so their resting metabolic rate is similar – we might say their pace of life is similar – then the bird lives 3 or 4 times

longer than the mammal. In some cases the discrepancy is even greater. Thus the resting metabolic rate of a pigeon and a rat are similar, yet the pigeon lives for 35 years while the rat lives barely 3 or 4, an order of magnitude difference. We, too, live longer than we 'should' if our lifespan is plotted against our metabolic rate – like many birds, and indeed bats, we live 3 or 4 times longer than other mammals with similar resting metabolic rates. When I say that we could extend our lifespan to perhaps several hundred years, I am comparing us with the pigeon, which lives two or three times longer than us, relative to its own metabolic rate. Put another way, a pigeon doesn't live so much longer than a rat because it has slowed down its pace of life. Rather, a pigeon lives 10 times longer than a rat while maintaining exactly the same pace of living. There are, apparently, no strings attached.

An important point is that ageing is usually, but not inevitably, linked to disease. The rat suffers similar diseases of old age to us. Rats become obese, get diabetes, cancer, heart disease, blindness, arthritis, stroke, dementia, you name it; but they develop these diseases within a two or three year timeframe, and not over decades. Many birds, too, suffer from equivalent diseases, but always towards the end of their lives. There is unquestionably a link between ageing and degenerative disease, but the nature of this link remains speculative and disputed. There are few things we can say for sure. One is that the link is not chronological – it does not depend on a fixed passage of time, but is relative to the lifespan of the creature concerned. It depends on age, not time; and the rate of ageing is broadly fixed for each species. While there is plenty of variation around the average, it is still not too far from the truth to say, with the bible, that our allotted time in this world is three score years and ten. This allotted time comes from within: it is controlled by our genes in some way, even though it can be modulated to a degree by diet and general health. When asked what finding would make him question his belief in evolution, JBS Haldane answered 'a Precambrian rabbit'. Likewise, I will cast all my views on ageing through the window when I meet a centenarian rat. A rat may one day evolve to live for a hundred years but only after changing a good many of its genes. It will no longer really be a rat.

There is a second point about the link between ageing and disease that is even more pertinent to our own suffering: degenerative disease is not an inevitable aspect of ageing. Some seabirds, for example, seem to sidestep the diseases of old age altogether, and do not age as 'pathologically' as ourselves. Like the elves they appear to live long and healthy lives, and somehow avoid many of the afflictions of old age. Exactly what they die of is not known with certainty, but it seems the incidence of crash landings rises with age; presumably, despite not succumbing to degenerative diseases, they begin to lose muscle power and coordination. There is a hint that the 'oldest old' among humans – those who live well past a hundred – are also less prone to degenerative diseases, and tend to die from muscle wastage rather than any specific illness.

There have been hundreds of theories of why we age. I discussed some of these in Oxygen, from a broad evolutionary point of view. Suffice to say here that many of the attributed causes of ageing fall prey to the traps of causality and circular argument. Some say, for example, that ageing is caused by a fall in the circulating levels of a hormone like growth hormone. Perhaps; but why do such hormone levels start to fall in the first place? Similarly, others hold that ageing stems from a decline in the function of our immune systems. Certainly this is a factor, but why does our immune function start to decline? One answer might be through an accumulation of wear and tear over many years, but this answer, albeit popular, will not do. Why do rats and humans accumulate wear and tear at such different rates? Could not a rat shielded from the slings and arrows of outrageous fortune live to a hundred? Absolutely not! Its rate of ageing is determined from within. We each hold within ourselves a ticking clock, and the speed at which the clock ticks is determined by our genes. In the jargon, ageing is endogenous and progressive: it comes from within, and it gets worse over time. Any explanation must account for these traits.

Most proposed clocks don't keep good time. The telomeres, for example – the 'caps' on the end of chromosomes that wear away over our lives at a steady rate – display such divergent patterns across species that they can't possibly be the primary cause of ageing. I have already dwelt on the metabolic rate as another clock. This, too, is

commonly dismissed as the clock of life on the grounds that the relationship between metabolic rate and ageing can be badly distorted – as in the case of the pigeon with its long lifespan linked to a fast metabolic rate. Unlike the telomeres, however, these distortions offer deep insights into the underlying nature of ageing. The metabolic rate is a proxy, somewhat rough, for the rate of free-radical leak from the respiratory chains within the mitochondria. Sometimes the rate of free-radical leak is proportional to the metabolic rate, as among many mammals, but the relationship is not always consistent: there are many examples where the metabolic rate does not tally with free radical leak. Such transgressions potentially explain not just the long lifespan of birds, but also the exercise paradox – the fact that athletes, who consume far more oxygen than couch potatoes, do not age any faster, and indeed often age more slowly.

As an explanation for ageing, free-radical leak from the mitochondria has been challenged repeatedly, and to convince must overcome a number of apparent paradoxes. Yet overcome them it does. The shape of the mitochondrial theory of ageing has transformed radically since its first exposition, more than 30 years ago. In its latest incarnation, however, it explains not just the broad outlines of ageing, but also many specific aspects such as muscular wastage, persistent inflammation and degenerative diseases. In this chapter, we'll see that the mitochondria are not only the main cause of ageing, but given the traits we have discussed in this book, it is inevitable that they should be. We'll also see what might be done about it, in our efforts to age with the grace of an elf.

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