DISPATCH

Evolution: Escaping the Inevitability of Ageing

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William Hamilton argued that even species inhabiting the farthest flung corners of the universe should age. However, a recent study shows that to find a species that escapes aging, you only need to look as far as your local pond.

As we grow older, physiological performance starts to decline, fertility falls and our risk of dying increases — changes we commonly call ageing. Humans aren't alone in ageing. Birds, mammals, insects [1] and even bacteria [2] all experience senescence, an age-associated increase in mortality and decline in fertility. Understanding the evolution of senescence was once seen as the greatest challenge in evolutionary biology and our current understanding of it hinges on the idea that once organisms begin reproducing, natural selection progressively weakens [3]. To understand why, consider an organism that reproduces steadily and has a fixed probability of dying. As this organism grows older, more and more of its reproductive success will lie behind it. This means that the fitness costs of any event that reduces survival or fertility will be less severe the later in life they occur. This weakening of natural selection late in life allows the accumulation of mutations with negative late-acting fitness effects (mutation accumulation [4]) — weaker selection is less effective at removing bad mutations — and favours alleles with positive effects on fitness early in life, even if there are costly side effects later on (antagonistic pleiotropy [5]).

Selection is also likely to favour high investment in reproduction early in life, even if this is at the cost of reduced investment in somatic maintenance later (disposable soma [6]) precisely because of the disproportionate contribution of early-life reproduction to fitness. The expected weakening of natural selection over time lead one of the greatest evolutionary thinkers, William D. Hamilton, to suggest that senescence is inevitable even in the "farthest reaches of almost any bizarre universe" [7], and this suggestion has almost become dogma. The problem is that it probably not true and in a recent paper, Schaible and colleagues [8] provide the most compelling evidence yet that at least one species, the freshwater Cnidarian *Hydra*, escapes senescence.

If you look closely, you might find *Hydra* in your local pond (Figure 1). Each adult, just a few millimeters long, attaches by its basal foot to underwater structures. Above the foot is the main body, consisting of two epithelial cell layers bordering a central gastric cavity, rising to a mouth surrounded by tentacles. While this is a simple body plan, it is dynamic. Body cells continuously divide and as they do so, push surrounding cells towards the top or foot of the body, where they differentiate [9]. However, because adults maintain a fixed size, as cells differentiate into new tissue, old cells are lost from both ends of the animal [10], or are allocated to offspring that bud asexually from a parent. Because of this regeneration through continual cell replacement, there has been speculation that *Hydra* might be immortal [11]. This idea received support when Martinez [12] found that *Hydra* appeared to escape senescence. In a four-year study, mortality risk in *Hydra vulgaris* was constant and very low. Importantly, although fertility fluctuated, it did not show age-associated declines. These data were striking but not compelling enough to really challenge the long-held idea that senescence is inevitable. After all, perhaps four years is simply not long enough to see senescence?

To resolve this uncertainty, Schaible and colleagues [8] studied *Hydra* on an unparalleled scale. The team studied senescence in individual *Hydra,* and in groups (genets) that share a common genome (because they belong to the same asexual lineage). Over eight years ago, a team in Germany established the first of nine cohorts of *Hydra magnipapillata* from genets that were over 33 years old. A second

team in California initiated three cohorts of *Hydra vulgaris, one* from a very young genet (< one year old), and two from unknown age. The research teams monitored survival and asexual reproduction in 2256 individual *Hydra* in an experiment spanning eight years. The results are striking.

None of the 12 *Hydra* cohorts showed an age-dependent rise in the risk of death, and mortality was very low throughout the experiment. In 10 of the 12 cohorts, on average, only one of every 167 *Hydra* died each year, and in two other cohorts mortality risk was even lower. Mortality risk did not vary depending on whether cohorts were established from old or young genets or as a function of parental age. Given this low mortality, the authors predicted that to really wrap up their study and observe the last *Hydra* die, the experiment would need to run for about 3376 years! As well as avoiding age-dependent rises in mortality risk, fertility did not decline over time either. While offspring production rates varied, the environment, rather than *Hydra* age, best explained these fluctuations. Taken together, *Hydra* did not show signs of senescence either at individual level, or at the genet level across strains, laboratories or cohorts.

Does this result really mean that *Hydra* escape senescence? Perhaps senescence only begins after eight years? However, according to two evolutionary theories of ageing, senescence should begin shortly after sexual maturity [4,5]. This is clearly not the case in *Hydra*, which have short pre-reproductive periods of as little as 5-10 days [12]. The 'disposable soma' theory [6] allows for a later onset of senescence but also assumes that there is a clear distinction between germ and somatic cells, which is not the case in *Hydra* [13]. At the very least then, these data show that the onset of senescence in *Hydra* is delayed far beyond theoretical expectations. This alone takes some explaining.

The study by Schaible and colleagues [8] adds to a growing body of data showing that age-dependent mortality and fertility do not always follow a senescent trajectory of decreased performance with age. Recent comparative analyses of dozens of animals and plants show that in some species mortality risk and fertility stay constant over time (negligible senescence) or mortality can even decline as fertility rises with age (negative senescence!) [1,14]. How can we explain this

diversity? Clearly variation in the strength of selection is important, and experimentally altering the strength of selection can change rates of senescence [15]. However, the most important advance in our understanding of variation in senescence is that natural selection does not always weaken as organisms age. Using reasonable, mathematical indicators of the strength of age-dependent selection that differed to those chosen by Hamilton [3], Baudisch [16] showed that selection strength can decrease, stay constant or even increase over the life-course. And importantly, if natural selection does not get weaker over time, then senescence is not inevitable. One factor that determines whether selection grows weaker or not, is likely to be whether a species continues to grow over its life-time (as larger, older organisms can be more fecund and hence late reproduction can be increasingly important). Building on these insights, optimization models incorporating growth trajectories and trade-offs between reproduction, growth and somatic maintenance show that in theory, negative and negligible senescence are possible evolutionary outcomes [17].

From a proximate point of view, how might *Hydra* escape senescence? Their impressive regenerative abilities may be crucial. Old cells, which might contain damaged DNA, are continuously lost from the distal ends of *Hydra*. Perhaps this allows *Hydra* to shunt off the damaged genetic material that the rest of us are lumbered with? Alternatively the answer may lie in their capacity to mend damage, as *Hydra* can repair their bodies even when cut in two. Studying species with unusual mortality profiles, such as *Hydra*, offers insight into the mechanisms that are (or are not) at work to delay or suppress senescence, and this has clear importance as human populations age.

What is clear from Schaible and colleagues' [8] work is that some species do not follow the senescent trajectories we expect. As yet, we do not fully understand why this is so, and this uncertainty has once again moved ageing into the top tier of evolutionary phenomena requiring further exploration.

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Figure 1. Forever young?

An adult green *Hydra* (*Hydra viridissima*) clearly showing the simple body plan. Photo: Frank Fox, www.mikro-foto.de.