Why Age?

By Silvan Urfer. Originally published in German and French in the Irish Wolfhound Club of Switzerland Bulletin 67/12; first publication in English in Harp & Hound 2/2012.

Why do we age? The process by which a fertilized egg turns into an adult organism is almost indeterminably complex – an organism capable of mastering such a difficult task surely should not have much of a problem to maintain its own function indefinitely. Nonetheless, we all know that this is not the case in practice. The reasons why are a subject of current research.

Why do we age at different speeds? An adult human being and an Irish Wolfhound are roughly the same size and have roughly the same metabolic activity, yet the human lives about ten to twelve times longer than the dog. Whoever has seen a few veterans' classes also knows that different lines of our breed seem to age at different speeds: In these classes, we can observe six-year-olds that look ancient next to ten-year-olds that look considerably younger than their colleagues who are, in reality, four years younger than them. Much of this is determined genetically; some of it is environmental or coincidental. The genetic part can be influenced through selection, both for better and for worse. The fact that very few breeders consciously select for the phenotype "aging process" betrays the fact that nearly all of them do so subconsciously. We will talk about this point later.

I do not pretend to be able to exhaustively explain all the whys and hows of aging within the scope of this article – currently, whole hordes of scientists are busy figuring out these problems. What I would like to do is provide a short overview of the theoretical and practical aspects of aging that are currently being discussed in the scientific community and then explain how they may apply to Irish Wolfhounds and their breeding.

Evolving blindly

The great biologist J.B.S. Haldane once said that *"nothing in biology makes sense except in light of evolution"*. If therefore we observe a biological trait in nature, we can be very certain that this trait brought an evolutionary advantage to the animals that exhibit it. According to this theory, as universal a phenomenon as aging should therefore have evolutionary advantages.

However, the notion that aging must convey an evolutionary advantage is not necessarily correct. As an example, we can have a look at Huntington's disease: a simple autosomal dominant trait that is always deadly, which is obviously not advantageous for the affected individuals. This begs the question why evolution has not been able to eliminate Huntington's from our species long ago. The answer is simple: Its first symptoms usually appear between the ages of forty and fifty – at an age at which most of the affected people have already had children.

The same is probably true for the aging process: Whatever happens to an organism after it has reproduced is not seen by evolution – it is literally blind in this regard. The fact that all higher organisms age is therefore not necessarily an indication that aging

is beneficial in itself – merely that there is no selection against aging as long as an individual reproduces sufficiently early and successfully.

Nevertheless, we should ask the question why aging is universal – after all, “no selection against” is not the same as “selection for”. For example, there is probably no selection against baldness in humans, yet not everybody becomes bald. There is also no selection against grey brindle in Wolfhounds, yet not all of them are that color. Aging, as a universal process, must therefore have additional causes. This brings us to the next chapter.

Too much of a good thing

When one gene has more than one effect on an individual, this is called *pleiotropy*. If these effects work against each other, we speak of *antagonistic pleiotropy*. This notion is fundamental to the modern understanding of aging, which is why we should discuss it a bit more exhaustively despite its name.

As we have seen, the goal of evolution is successful reproduction: Whoever has the most progeny has reached evolutionary success, and the responsible genes have a better chance of still being present in the gene pool of a species over the subsequent generations.

As an extreme case, we can consider some species of Australian marsupial mice (*Antechinus* spp.) They only reproduce once a year: During mating season, the males mate with the females frequently – so frequently and vigorously, in fact, that by the end of mating season, all of these males die of stress and exhaustion. The very genes that ensure their reproductive success thus also cause their early demise. These mice are a textbook example of antagonistic pleiotropy, in which genes favoring early and intense reproduction at the same time decrease overall survival. Nevertheless, evolution favors these genes, as the evolutionary success of an individual is defined by the number of its progeny.

The marsupial mouse is an extreme example of a process that occurs in all higher organisms, albeit usually in somewhat less dramatic form: For example, growth hormone is beneficial during youth, where it mediates growth and improves muscle strength, but at a later age becomes a risk factor for diabetes and can also cause diseases such as acromegaly. Sex hormones such as testosterone improve strength and general well-being, but also increase the risk of heart attacks and strokes in the long run. Organ regeneration through stem cells is beneficial in case of injury, but also increases the overall risk of cancer. The disappearance of the thymus during early adulthood prevents autoimmune disease, but also renders the immune system less efficient later in life. These are all examples of antagonistic pleiotropy: Traits that convey an advantage early in life and thus are selected for by evolution can turn into disadvantages in the long run and lead to the changes we know as aging. Therefore, aging can indeed be described as “too much of a good thing”.

Aging creatures great and small

Antagonistic pleiotropy thus explains why aging is universal: It is selected for indirectly through the selection of traits that are advantageous in young individuals

and improve reproductive success, but can become deleterious in the long term. This explains succinctly why all higher animals are subject to aging. Nevertheless, there are significant differences between species and also within the same species:

We know for example that a Labrador Retriever is old at ten years of age, a horse at twenty and an elephant at sixty. However, we also know that a seven-year-old Yorkshire Terrier is not biologically as old as an Irish Wolfhound of the same age. These observations can be generalized into two rules of thumb:

1. **Small species age faster than large species.**

2. **Within the same species, large individuals age faster than small individuals.**

There are several explanations for this apparent contradiction. The most widely accepted one is the *Rate-of-Living* theory first put forward by Rubner in 1908: It states that the maximal lifespan of a cell is limited by the accumulation of toxic metabolic products and DNA damage. The faster an organism's metabolism runs, the faster this accumulation takes place, thus determining the speed of the aging process.

This theory explains fairly well why larger species generally age more slowly than smaller species: A horse's or an elephant's metabolism works more slowly than a dog's or a mouse's; therefore, horses or elephants age more slowly than dogs or mice and thus have a longer life expectancy. The theory can also be confirmed experimentally: If we keep one colony of fruit flies at a lower and one at a higher temperature, the flies that are kept in the cold have a slower metabolism and a longer lifespan than those that are kept warm. Also, mice, rats, monkeys and dogs that are fed a low-calorie diet have been shown to have a lower body temperature, a slower metabolism and a significantly increased lifespan as compared to control animals fed a regular diet.

The fact that within the same species, large individuals age faster than small individuals is also explained by *Rate-of-Living* theory: During the growth period, the metabolism is more active than during adulthood. Large individuals grow faster and longer than small individuals, thereby exerting a greater metabolic expenditure than smaller individuals. This means that there is more damage present in their cells at the end of growth than there is in small individuals, and accordingly, their overall life expectancy is diminished.

One fact supporting this theory is that age-related cataract is considerably more common in large dogs than in small dogs of the same age. More evidence is provided by taking cells from young adult large and small dogs and growing them in culture: The large dog cells die after fewer cell divisions than those taken from small dogs of the same age, indicating that they have fewer reserves at the end of growth.

Small difference

Rate-of-Living theory thus provides a useful and logically sound explanation for many of the correlations that we can observe between body size and the rate of aging. Unfortunately, there is a catch: Plenty of species seem to ignore it completely.

Opossums, for example, are about the size of a cat or a small dog, yet they die of old age at less than two years. The coastal mice in the genus *Peromyscus* are about the same size as our house and lab mice, yet they live twice as long. The naked mole-rat *Heterocephalus glaber* is about the size of a Guinea pig, yet it can live for more than 30 years. The bat *Myotis brandti* weighs around seven grams and lives for more than 40 years. Finally, the clam *Arctica islandica* weighs around 50 grams and has a documented maximal lifespan of well over 500 years![1]

Even if we ignore the last example for the moment and stay within mammals, we can easily see that *Rate-of-Living* theory is not a sufficient explanation for these differences in the speed of aging between species of roughly the same size. Neither does it explain the wide variety in the speed of aging that we can observe between different lines of Irish Wolfhounds.

The questions of why and how can be asked in two different ways: Which differences in metabolism are present between short-lived and long-lived species? And why did these differences evolve over time?

If we compare metabolisms between short- and long-lived species, we find that the proteins in the cells of the long-lived ones are considerably more stable and resistant to oxidative and other kinds of stress than they are in short-lived species and also react less strongly to external damage. Nuclear proteins in particular seem to be considerably more stable in long-lived species. These variants in protein structure are determined genetically – therefore, there is a genetic base for the fact that some species age faster and some more slowly. Of course, this also implies that such genetic differences in protein structure can also exist between different individuals within the same species.

Eat and be eaten

The evolutionary perspective is slightly more complicated. As we have already seen above, evolution is not particularly concerned about a longer lifespan as long as an animal has a large number of progeny early in life. Given that most wild animals do not die of natural causes, but are eaten by predators, being able to reproduce at a young age conveys an evolutionary advantage by helping them to maximize the number of their progeny and thus their reproductive success.

As we have also seen above, genes that favor fitness and fertility during youth can turn against the animal as it ages by means of antagonistic pleiotropy – hence, such an animal can be expected to age more quickly than an animal that may be somewhat less fit and/or fertile at a young age.

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[1] *For more comparisons between the life expectancies of different species, I can recommend João Pedro de Magalhães' web site: http://genomics.senescence.info/species/index.html*

This can turn into an evolutionary advantage if an animal can live long enough to go through more reproductive cycles than an animal that is more fertile at a young age, but ages faster. The lower number of progeny per cycle that helps increase lifespan by reducing antagonistic pleiotropy is more than compensated for by the higher number of cycles in these animals and can thus be evolutionarily favorable by increasing overall reproductive success – but only if the pressure exerted by predation is sufficiently low to allow a significant number of these animals to go through more than one reproductive cycle.

Again, the opossum provides an example for this mechanism: Dr. Austad has studied the maximal lifespan of mainland opossums and compared it to a population that has been isolated on an island without predators for at least five thousand years. In the wild, almost no mainland opossums live long enough to have more than one litter, as most of them get eaten by predators. On the island, however, a significant number of individuals get to have a second litter – the genes that favor a longer fertile period are therefore advantageous for overall reproductive success in this population.

If we keep opossums from both populations in captivity and measure their fertility and natural lifespan, we find that the island opossums have smaller litters on average, but live about 30% longer than the mainland opossums. Natural selection favoring a second reproductive cycle thus leads to a decrease in fertility per cycle and simultaneously increases overall lifespan. In the mainland population, which faces high predatory pressure, having one large litter is an evolutionarily more successful strategy than trying to have two smaller litters; however, in the island population, the increased chance of having a second litter more than makes up for the smaller size of both litters.

The same mechanism is also at work in coastal *Peromyscus* mice, which occur on small islands with few predators and on average live twice as long as our house and lab mice, which evolved under high predatory pressure. The naked mole-rat lives subterraneously and is therefore better protected from surface predators than the Guinea pig (on a side note, the naked mole-rat is interesting in that there has never been a tumor found in this species in thousands of necropsies). Bats are protected from snakes and other terrestrial predators due to their ability to fly, and a flying lifestyle also requires comparably small litters, leading to an evolutionary advantage in having a longer reproductive period. Finally, the clam *Arctica islandica* is a deep-sea-dweller, where there are virtually no predators and where the ability to undergo an ever-increasing number of reproductive cycles more than compensates for the smaller number of progeny per cycle.

We can therefore summarize:

1. **The aging process is faster in species that are subject to a high selection pressure from a young age onward and are therefore forced to reproduce young.**

2. **In an environment where the ability to reproduce later in life creates an advantage, animals evolve a slower aging process.**

These predictions can also be confirmed experimentally: If we breed fruit flies in a lab (mean lifespan: 14 days) and only let them reproduce after the age of two weeks, we decrease the number of eggs per clutch, but at the same time, we also double the flies' life expectancy within 13 generations! (Michael Rose) As discussed, the underlying evolutionary mechanism is antagonistic pleiotropy: Higher fertility at a younger age leads to faster aging later in life, while sustained fertility later in life favors slower aging.

On a side note, this mechanism is probably also involved in the differences in life expectancy that we can observe between small and large species: Larger species have fewer predators and furthermore, their population density is also lower than it is in smaller animals, which leads to a lower risk of disease transmission within the species. All of this decreases the evolutionary pressure that favors early reproduction: a larger number of reproductive cycles constitute an evolutionary advantage in such species, which in turn favors the evolution of a longer lifespan.

Finally, this mechanism also explains why we as human beings generally live longer than elephants or horses, even though we are considerably smaller: Our technology (from stone-age bows and arrows all the way to modern hunting rifles) has decreased the evolutionary pressure that predators exert on our species for thousands of years – not to mention the advantages of modern medicine.

Consequences – looking at Irish Wolfhounds

If, after these considerations, we look at the situation in Irish Wolfhounds, we notice that our breed is subject to several inherited diseases that first show symptoms at an age when most dogs have already had progeny and/or earned their champion title (cardiomyopathy, osteosarcoma, epilepsy etc.) – diseases that therefore need not be much of a concern to a breeder who is mainly interested in producing puppies and winning at dog shows. However, breeders who value their dogs' health cannot be sure either that their breeding animals will not develop cardiomyopathy or maybe epilepsy at age four of five. Given that our dogs' fertility tends to decrease over time, breeders nevertheless breed them at an early age, and if such problems then show up later – there is not much they can do about it!

If therefore some breeders use their dogs and bitches as young as possible because they fear that they will not be sufficiently fertile later in life, they do in fact subconsciously select for dogs that have a high fertility early in life – and thereby, just as subconsciously, for a lower lifespan due to an increase in antagonistic pleiotropy. The same is presumably the case for breeders whose dogs already look entirely mature at 18 months of age: Whoever grows up quickly and becomes fertile early also ages quickly. By selecting for early fertility and maturity, allowing dogs to become champions at less than two years of age, they also select for a faster aging process and thus for a lower lifespan. This in turn increases their incentive to finish and use their dogs for breeding even earlier, which again selects for even better fertility at a young age, as well as faster maturity – and we have thus created a situation in which the abysmal life expectancy of our breed has become a self-maintaining and self-reinforcing process: a vicious circle!

If we were to only breed dogs above five years of age, the problem of DCM at least would become history within one or two generations. As far as bone cancer and epilepsy are concerned, this would presumably take longer, as their modes of inheritance are more complex.

Given that we cannot realistically expect most breeders to follow such a method, we should instead pay more attention to antagonistic pleiotropy: Dogs that look mature and adult at an early age are probably not particularly desirable as breeding stock if one is to select for better longevity. Instead, dogs that only look fully adult at age four or five are to be preferred. Also, old males whose sperm has been frozen at age two or three are presumably less valuable in selecting for longevity than males and females who have demonstrated their fertility at an advanced age. By selecting for fertility late in life, we can expect to improve our dogs' life expectancy through the associated reduction in antagonistic pleiotropy. I do not pretend that we will be able to double their lifespan within 13 generations like it is possible in fruit flies – but a significant improvement of the current, abysmal situation is both desirable and quite probable.