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The Death of Death N°177
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Imagine a rather educated mouse wondering whether it's theoretically possible to live longer than the average life expectancy of two and a half years? Of course, it's possible," she'd say, "just look at the human species (...), mammals like us who live thirty to forty times longer! (translation) Au-delà de nos limites biologiques: Les secrets de la longévité. 2011. Miroslav Radman.

This month's theme: Different lifespans of animals: Very long, very short, in the real world and the labs

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Most people consider a lifespan of 80 years as something logical and good. If our normal lifespan was 20 years or 300 years, we would probably regard it as logical and good as well. Philosophers and religions would explain convincingly why shorter or longer lives would be bad.

A normal lifespan for animals with senescence can vary in extreme ways, from a few days to a few centuries. There are even some specific animals that never age and can live for thousands of years and others who die before they are born. Concerning our close cousins mammals, the variation goes from two to two hundredth years. In this newsletter, we will approach animals with the longest life, and with the shortest lives and animals we study in the laboratories to understand their longevity.

Biologically immortality

Biological immortality means no irreversible senescence. This implies, among other things, that fertility is not decreasing with age. It has been said of quite a few animals. However, systematic observation for centuries is impossible and in most cases of affirmation of biological immortality, no lifespan of centuries is proved.

It can be noted, concerning life outside of the animal reign, that some plants, especially some trees, but also posidonia, and unicellular living beings seem biologically immortal.

Turritopsis nutricula

Turritopsis nutricula, commonly known as the "immortal jellyfish," has captivated the scientific community due to its extraordinary ability to reverse its aging process and potentially achieve biological immortality. This unique jellyfish species, found in oceans worldwide, starts its life as a polyp, an underwater life form attached to the seabed. As it grows, *Turritopsis nutricula* gradually transforms into a jellyfish. In times of difficulty, it can regress to the polyp stage before transforming back into a jellyfish, capable of repeating this cycle indefinitely. This organism can reverse its mature cells back into their earliest form, essentially restarting its life cycle. Of course, the concept of biological immortality is complex but the remarkable rejuvenation ability of *Turritopsis nutricula* offers fascinating insights into the possibilities of life extension in the animal kingdom.

They are other animals (and plants) who do not show senescence. However, most of those animals (and of course plants) do not have a brain. Glass sponges, some corals, and maybe tubeworms can reach thousands of years. Hydra's, planaria also do not seem to age, at least for the individual reproducing asexually. Lobsters also do not age. But they also do not stop growing and they will die at one moment because they become too big to survive. Tardigrades seem not to age when in cryptobiosis. Rougheye rockfishs and naked mole rats (see below) are also sometimes mentioned as biologically immortal but with no animal older than 100 known.

Very long life

The main characteristics of animals living very long are big size, low metabolism, and few predators. But not all those characteristics are necessary for very long-living animals. In general, vertebrates flying or living underground (for example olms in caves) tend to live longer.

Greenland shark

The Greenland shark, scientifically known as *Somniosus microcephalus*, is renowned as the longest-living vertebrate globally, with estimated lifespans of up to 512 years. Inhabiting the Arctic and North Atlantic waters, they don't reach sexual maturity until they're over a century old. These sharks owe their exceptional longevity to factors such as a slow metabolism and their cold-water habitat. This extended lifespan presents a unique opportunity for scientists to delve into the biological mechanisms behind their remarkable longevity, offering valuable insights into aging and adaptation in extreme environments.

Whales

The only mammals living longer than humans are whales. It is somehow logical for one of the biggest animals in the world, with no predator when adult. They probably can live more than 2 centuries.

Tortoises and sphenodons

The extreme longevity of some tortoises, especially coming from the Galapagos is well-known and logical for animals of a big size, with no predators before humans came and a low metabolism. The oldest living turtle is 192 years old.

Less well-known are the Tuatara's (sphenodons) who can live and lay eggs after more than one century.

Grey parrots

Parrots, known for their exceptional cognitive abilities and unusually lengthy lifespans, until 83 years, may correlate with these traits, according to a study led by Max Planck researchers. The study examined 217 parrot species, including well-known ones like the scarlet macaw and sulfur-crested cockatoo, which exhibit remarkably long lifespans of up to 30 years, typically observed in larger bird species. The researchers proposed a potential explanation for this longevity: a significant correlation between large relative brain size and extended lifespan.

Albatrosses

A Laysan albatross named Wisdom is the oldest known wild bird (more than 70 years). It is also the bird to have laid an egg at the oldest age: 68.

Bats

In contrast to various aging theories, bats, despite their elevated metabolic rate, exhibit remarkable longevity, living approximately three times longer than other mammals of comparable size. The mystery surrounding how bats achieve this extended lifespan has garnered significant attention, often drawing parallels to immortal fantasy figures like Dracula from Bram Stoker's novel. Numerous ecological and physiological characteristics, including diminished mortality risks, delayed sexual maturation, and the ability to hibernate, have been associated with the prolonged lifespan observed in bats. Despite these insights, there remains a scarcity of information regarding the specific molecular mechanisms that contribute to the exceptional longevity observed in bats.

Eusocial insects and larvae.

Queens (this means reproductive females) and sometimes kings (reproductive males) of eusocial insects like bees, ants, and termites can live a much longer life than most insects. The record is 8 years for bees, for ants almost 30 years, and for termites, it is roughly 30 to 50 years. What is particularly interesting for those animals is that so-called workers or soldiers have often the same genes, but live lives tenths of times shorter. It would be interesting to know if some mechanisms allowing a much longer life for some insects can somehow be duplicated by mammals.

Some insects have a very long life as a larva. The longest normal larva period concerns periodical cicadas living 17 years as a larva (and then massively becoming adults to limit predation). Splendour beetles can be larvae during an even longer period. The longest recorded period is 51 years.

Very short lives

We wrote that animals with a very long life have usually a big size, a low metabolism, and few predators. Unsurprisingly, animals with a very short life are usually small, with a fast metabolism, and with many predators.

Some of those animals (C Elegans, drosophila, Nothobranchius, mice, and rats are studied in the laboratory and will be approached in the third part of this newsletter.

Many insects are considered to have a very short life but have a longer life during their larva phases. The famous mayflies who live only days, even hours or minutes as an adult and many species of butterflies who do not eat when they are adults have a nymphal of several months to several years,

The strange (non-)life of some mites.

The strangest shortest known lifespan is the life of males Acarophenax tribolii. Their lifespan is less than nothing because they die before they are born! The mother Acarophenax produces young in a ratio of 15 females to one male. The male copulates with all its sisters during gestation and dies when still in the womb of the mother. The mother later literally explodes and dies, releasing her young daughters already pregnant. And the cycle starts again, they will grow and give birth by exploding.

Gastrotrich

It is a very small worm-like animal found in freshwater areas everywhere in the world. The whole lifecycle can happen in 2 days, but it can also be longer than 40 days.

Chameleons

The terrestrial vertebrate with the shortest life is the Labord's chameleon. He normally lives less than 6 months. It is an interesting animal because other chameleons, genetically probably not very different, can live up to 10 years. However, it must be said that apparently in favorable situations, some animals live longer.

Mammals. The shrew and the male antechinus.

The mammal having the shortest life for males and females is the common shrew. This very small carnivore animal will normally not live longer than one year. It is less than rats and mice that are abundantly suited for longevity, but far less easy to breed.

The male antechinus is a small marsupial that lives less than one year, dying during or just after the period of reproduction. This is sometimes called "suicidal reproduction".

Animals in the laboratories

From widely used model organisms like fruit flies (Drosophila melanogaster) and nematode worms (Caenorhabditis elegans) to more complex mammals such as mice and rats, researchers explore various species to understand the genetic, physiological, and environmental factors influencing lifespan. Additionally, unconventional subjects like bats and parrots have recently captured scientific interest due to their exceptional longevity despite high metabolic rates. These animals serve as valuable models to investigate the intricate mechanisms that contribute to prolonged lifespans, shedding light on potential insights applicable to the broader spectrum of life, including humans.

Roundworms

Caenorhabditis elegans is a roundworm with a 20-day lifespan, making it a good subject for research. More than 400 genes that extend lifespan in roundworms have been described. Among the genetic controls studied are a series of interacting proteins that act like insulin and control reproduction and longevity. Investigators have also looked at a mechanism controlled by a group of genes called clock genes. These regulate metabolism in the roundworm and affect lifespan. The roundworm genes that seem. to confer increased longevity do so by supporting resistance to external stresses, such as bacterial infections, high temperatures, radiation, and oxidative damage. The correlation between the existence of roundworm genes and their mammalian counterparts suggests that the roundworm will continue to be a valuable animal model for the study of aging.

Fruit flies

Drosophila melanogaster, or the fruit fly, is a favorite subject for studies on longevity. Researchers have identified one gene that they have named Methuselah, which can increase fruit fly life span by 35 percent. Molecular physiologist Xin-Yun Huang of Cornell University's Weill Medical College in New York City has been conducting research to uncover what activates the Methuselah protein. Huang and his team found that another protein, the Sun protein, binds to Methuselah and alters fly longevity. Flies with a disabled copy of the Sun gene lived 50 percent longer than control flies. A number of studies on a fruit fly gene called Indy (for "I'm Not Dead Yet") have been published. Because the fruit fly has genes such as Indy that produce proteins very much like human proteins, it makes an excellent animal model for aging research.

Nothobranchius furzeri

The Turquoise killifish is an extremely interesting freshwater fish for the study of aging. It is easy and not expensive to breed. It is so easy and nice that people keep it as a pet. It has also the shortest life of all vertebrates but one (Eviota sigillata, a sort of Gobi). The Kill fish has remarkable capacities for regeneration but will live for a maximum of twelve weeks. Hundreds of scientists around the world are studying the animal to try to understand and solve the fascinating questions of senescence. They do not study as much Eviota sigillata who live an even shorter life of a maximum of 59 days, because breeding this small saltwater fish is far more complicated. Another fish that must used for scientific studies is the Zebrafish, because of its capacity for regeneration. This animal can live up to 5 years in an aquarium.

Muridae

Mice and rats are the favorite subjects of scientists interested in human aging. Because they are mammals, they are more closely related to us than yeast, flies, or worms, and their relatively small size and short life span make them easier to study than long-lived animals. Much of the excitement in recent aging research has come from discoveries that aging can be postponed in mice or rats by very low-calorie diets and by discoveries of mutant genes that can extend life span by as much as 50 percent. Through targeted genetic manipulation, researchers have already created genetic lines of mice that model Werner's syndrome (premature aging), Alzheimer's disease, other neurodegenerative conditions, atherosclerosis, diabetes, immune dysfunction, musculoskeletal disorders, oxidative stress, and many other medical conditions associated with aging. Other studies are using mice engineered to make them particularly vulnerable to DNA damage or damage to their mitochondria (energy-producing "organs" inside cells). The growing interest in mouse aging and genetics has been strongly stimulated by the sequencing of the mouse and human genomes and by the realization that most human genetic diseases can be modeled by changes in equivalent genes in these rodents.

Naked Mole Rats

Those rodents already studied in a recent newsletter are living exceptionally long lives for a small mammal. They live in underground colonies and are relatively easy to observe in captivity. Contrary to all other well-studied vertebrates, they seem to show no senescence in the sense that their probability of dying does not seem to progress with age. However, they show other signs of aging.

Dogs

The distant children of wolves have lived with us for so long that they acquired good and bad habits. They are so culturally and physically close to us that they are ideal to compare with us. And since we have millions of them of old age, it will be extremely easy to start experiments on longevity with animals of old age. It could even be in combination with treatments with their well-informed owners.

Nonhuman Primates

The discovery that fruit flies and roundworms carry genes that affect their longevity is exciting, particularly because many of those genes have human counterparts. However, the fact remains that the complexity of human physiology can't be replicated in simpler organisms such as fruit flies and roundworms. But our DNA is very similar to that of nonhuman primates such as monkeys and apes. And it is nearly identical to that of chimpanzees. The National Institute on Aging (NIA) is sponsoring an extensive series of experiments into aging and longevity using primate models, including rhesus and squirrel monkeys. Rhesus monkeys are particularly useful because the rate of aging in rhesus monkeys is three times as fast as the rate in humans. It is important to say, in ethical terms, that the goal and result of the experiments is to allow a longer and healthier life for primates and consequently for humans. Primate studies are ongoing in neurobiology, skeletal deterioration, reproductive aging, and other age-related diseases such as heart disease and diabetes. Results from studies of caloric restriction and its impact on aging in primates are also available.

The good news of the month: LEVF experiments are progressing

The Longevity Escape Velocity Foundation is pursuing an experiment on 1,000 mice. After about 10 months, the results are already very promising, especially concerning the female mice with a big difference in mortality between mice with no treatment and mice with all treatments.

A second study is in the preparation mode, subject to. The interventions would be: Deuterated Fatty (Arachidonic) Acids, Mouse Serum Albumin, Mesenchymal Stem Cells, and Partial Cellular Reprogramming

It is to be hoped that the LEVF will soon not be anymore the only working longevist organization working on a large number of old mice observed until their death with a promising treatment. Organizations like Hevolution, Google Calico, the Chan Zuckerberg Foundation, and Altos Labs should use a few million dollars among their billions to test their most promising ideas on our mammalian short-living far cousins.

For more information

- Heales, Longevity Escape Velocity Foundation, International Longevity Alliance, Longecity, and Lifespan.io
- Heales Monthly Science News
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