



HAL
open science

Lifespan Versus Healthspan

Eric Le Bourg

► **To cite this version:**

Eric Le Bourg. Lifespan Versus Healthspan. Jonathan Sholl; Suresh I.S. Rattan. Explaining health across the sciences, vol 12., Springer, pp.439-452, 2020, Healthy Ageing and Longevity, 978-3-030-52662-7. 10.1007/978-3-030-52663-4_25 . hal-02927140

HAL Id: hal-02927140

<https://hal.science/hal-02927140>

Submitted on 1 Sep 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Lifespan versus healthspan

Eric Le Bourg

**Centre de Recherches sur la Cognition Animale,
Centre de Biologie Intégrative, Université de Toulouse,
31062 Toulouse cedex, France**

E-mail: eric.le-bourg@univ-tlse3.fr

Abstract

Lifespan is a measure of duration, not of content, and it does not provide the same information as biological markers of ageing. Therefore, one cannot rely on lifespan to infer conclusions about ageing. For example, two centenarians can die in very contrasted physiological states: as bed-ridden for years or during jogging. Healthspan can be measured in animal models by relying on behaviour, resistance to stress, and so on. Biogerontologists working with animal models tend to privilege the measurement of lifespan rather than that of healthspan when the animal lives for a short time (e.g. *Caenorhabditis elegans*, *Drosophila melanogaster*) because measuring lifespan is easy and studying, say, behaviour, is more difficult. Conversely, biogerontologists privilege healthspan when the animal model lives for years (e.g. rodents, non-human primates), because measuring lifespan can be out of reach. In any case, biogerontologists should try to observe both lifespan and indicators of health, whenever it is possible, and not conclude that ageing is delayed when they have simply observed longer lifespans.

Key-words

Lifespan — healthspan — animal models — non-human primates — human beings —

Introduction

This book is an attempt to precisely define what is health and how various sciences can help to define this concept. This is not an easy task and it has given rise to debates for decades, particularly since the major article by the philosopher Christopher Boorse (1977). The present chapter is concerned with health at old age and with the differences, or absence of differences, between lifespan and ageing. It is necessary to define, at least operationally, what is health in the context of ageing.

Pathology can be broadly defined as too long a distance from a mean functioning, and health as the variation, allowing the normal functioning of the organism, around the mean of a given trait (Boorse 1977). This statement implies that health is defined at the population level and not at the individual one: “Individual health is conformity to functional normality” (Giroux 2009). For instance, in human beings, a body mass index (BMI) in the 20-25 kg/m² range is a “healthy” variation, neither too lean nor overweight. Being in the overweight 25-30 kg/m² range can be less healthy, but 15 or 40 kg/m² BMI are clearly pathological because the sign of a disease (e.g. anorexia nervosa vs morbid obesity). However, being far from the mean is not always pathology. For instance, the Jeanne Calment’s 122 years lifespan (Jeune et al. 2010) is not a sign of pathology,

even if very far from the 85.4 years mean lifespan of French women in 2018 (Pison 2019). Boorse (1977) emphasised that “superior functioning is consistent with health. The unusual cardiovascular ability of a long-distance runner is not a disease”. However, the observed mean in a country can be unhealthy, such as for instance the mean BMI in the USA, with nearly 40 % of the adult population being obese with a BMI ≥ 30 kg/m² (Hales et al. 2018).

One could argue that the optimal value at old age of any trait should be that observed in young adults. However, this would imply that, for instance, because the growth hormone (GH) levels decrease with age (Roelfsema and Veldhuis 2016), it would be necessary to supplement older adults with GH even if they have no GH deficiency. It is not the case, because supplementation with GH as an attempt to delay ageing is associated with many risks, and thus does not improve health but just the contrary (Harman and Blackman 2004). Hence, it would be an error to consider any age-related change as a sign of lower health. For instance, the age-linked weight increase between 18 and 50 years of age does not increase mortality if weight remains in the 20-27 kg/m² range (Song et al. 2016). Therefore, the healthy range at old age is not necessarily the healthy range observed at young age.

It is needed to record not only lifespan, but also traits linked to health at old age, because lifespan does not provide the same information as biological markers of ageing. Lifespan is a measure of duration, not of content, and one cannot rely only on lifespan to infer conclusions about the ageing process. For instance, two centenarians could be either bedridden for years or jogging as every morning the day before their death and, thus, knowing the lifespan of individuals is not sufficient to know their physiological status or quality of life. Obviously, a human dying at 40 years of age from a non-accidental cause was probably not healthy.

Nevertheless, many biogerontologists who try to discover means to improve health at old age rely on lifespan as the gold standard to know whether their attempts were successful or not, even if some authors have warned against such a rationale (e.g. Le Bourg et al. 1993; Bansal et al. 2015; Briga et al. 2019). As emphasised by Briga et al. (2019), “the (implicit) assumption is often made that factors changing lifespan will consistently alter healthspan and senescence” and thus that an increased lifespan is similar to a delayed ageing process, and thus to a better health at old age. Conversely, a study reported that the oxygen-sensitive *mev-1* mutant of the nematode *Caenorhabditis elegans* has a high sensitivity to oxygen poisoning and a decreased lifespan in a 60 % O₂ atmosphere (Ishii et al. 1998). This decreased lifespan was called “premature ageing” by the authors. Therefore, according to them, a decreased lifespan is similar to an accelerated ageing process.

If a long lifespan does not imply being healthy when old, one can wonder why many

biogerontologists working with some animal models only measure lifespan. By contrast, clinicians mostly rely on measures of health at old age rather than on lifespan. The various constraints these scientists face when working with animal models can explain these different strategies to study ageing. What are the features of the different animal models when studying ageing and how these models can be of help in such studies? Let us consider the most widely used models: *Drosophila melanogaster* flies, the nematode *Caenorhabditis elegans*, the rodents *Mus musculus* and *Rattus norvegicus*, and the non-human primates *Microcebus murinus* and *Macaca malatta*.

Lifespan and healthspan in animal models

Lifespan and healthspan in Drosophila melanogaster flies

When biologists began to study ageing in *D. melanogaster* flies, more than one century ago, the study of behaviour or of life-history traits was in its infancy (but see below for rodents), precluding to observe the effects of ageing in individuals. In such conditions, the obvious best second choice was to focus on an easy, cheap, and straightforward measure — lifespan — and to assume that it was a *bona fide* surrogate of ageing. Lifespan is easy to measure, amenable to statistical analysis, and conceptually easy to understand. Indeed, if an animal dies at a young age, its death is more probably due to an accident or a disease than to the ageing process. By contrast, last survivors have a higher chance to die because of the natural failure of the organism, i.e. from ageing. Thus, many articles on the effects on lifespan of various treatments such as temperature, food, density of population, and so on, were published before World War 2 (e.g. Loeb and Northrop 1917; Pearl et al. 1927, Kopec 1928). These early experiments were maybe more of help to know the best ways to rear flies than to really understand the ageing process, as sadly emphasised by Pearl (1928): “In the aggregate many months have been spent in studying matters of fly husbandry, for the sole purpose of learning how to set up definitive experiments”. However, what was acceptable before World War 2 is not in the 21st century. Considering that a single number — lifespan — can summarise the whole process of ageing is an outdated view of biology and it is needed to observe not only lifespan, but also ageing, which can require observing animal behaviour.

The first study really observing the effects of ageing on the behaviour of *D. melanogaster* was probably that of Wigglesworth (1949) who showed that the mean “duration of flight to the point of complete exhaustion” of flies tethered by the thorax to the tip of a needle was 133 min (n = 13) in one day-old flies, 278 min (n = 14) in one-week-old flies, and 100 min (n = 21) in 4-week-old ones, no matter the sex. The absence of statistical analysis, the low sample sizes, the rounding of the last digit to 0 or 5 of values of 1 and 4-week-old flies, but not of those of 1-day-old ones, show that it was really an early, pioneering, study of behavioural ageing in flies. While some

studies of behaviour were done in the 1950s and 1960s, most of them only studied young flies and Elens and Wattiaux (1971) were maybe the first authors to study phototaxis in 5- and 30-day old flies. The number of studies greatly increased during the 1980s and Le Bourg (1988) published the first review article on age-related behavioural changes.

It could thus be expected that, nowadays, most biogerontologists record the behaviour of flies at various ages, but it is not the case. As emphasised by Grotewiel et al. (2005), “functional senescence, defined here as the intrinsic age-related decline in functional status, has received much less experimental attention in model organisms than life span” because “assessing death in survival studies is typically more straightforward than measuring a function across age”. Furthermore, when authors make use of a behavioural trait, many of them rely on a single one, the climbing ability. In this test, a number of flies is put into a vertical vial that is manually tapped to the bottom: the number of flies reaching a given height in a given time is recorded. For instance, Miquel et al. (1972) put 50 flies into a 250 ml vial, that was tapped 10 times on the bottom, and counted the number of flies reaching the 250 ml mark in 20 seconds. This test can be repeated with the same flies and the mean number of flies reaching the mark is the climbing ability measure (e.g. Seugé et al. 1985). However, this test has flaws. First, as the vial is manually tapped on the bottom the strength of the shock varies among experimenters or successive trials by the same experimenter. Second, many flies are in the same vial and, as the test can be repeated to get a mean score, it is impossible to know whether the same flies were reaching the mark or not, and if “interindividual interactions” could alter the climbing scores, as emphasised by Garcia and Teets (2019). To overcome these issues Le Bourg and Lints (1992) used individual flies with a test tube shaker providing always the same mechanical stimulation. However, the age-linked decline of climbing ability is so paramount and can be modified by so many factors that even the worst procedure will show age-related changes. As a result, climbing ability has become the most used behavioural test in research on ageing (review in Grotewiel et al. 2005), even if it is difficult to compare the results of studies using different procedures.

Beyond the climbing ability test, other traits linked to behaviour have been used in old flies, such as spontaneous locomotor activity, patterns of movement, habituation and learning of various tasks, memory, phototaxis, threshold to sucrose (reviews in e.g. Le Bourg 1988; Grotewiel et al. 2006; Iliadi and Boulianne 2010; see also Le Bourg 1996, 2004). Can it be possible to link individual measures of behaviour and lifespan of the very same flies, flies showing a “better” behaviour living longer? This is not the case when spontaneous locomotor activity is observed, at young age only of repeatedly throughout life: more active flies are not more or less longevous than less active flies (Le Bourg 1987, Le Bourg and Lints 1984; Le Bourg et al. 1984; Lints et al. 1984).

Similar results are observed when the patterns of movement in a circular arena are observed: the paths are more sinuous at old age, but there is no correlation between the shape of paths at young or old age and lifespan (Le Bourg 1985). Therefore, these behavioural traits are not predictive of lifespan.

Other indices of health can also be measured, as for instance resistance to severe stress as a function of age. This resistance can decrease in old flies and a delay in this decline or a better resistance could be considered as showing a slower ageing (e.g. Service et al. 1985). In addition, one could expect that a lower or delayed age-linked decline of these traits is linked with a longer lifespan. In some cases, this is observed. For instance, a mild cold stress at young age can increase lifespan, but it also delays the age-linked decline of climbing ability in males and increases survival time at 37 °C at old age (Le Bourg 2007). By contrast, overexpression of the gene of the antioxidant catalase enzyme increases resistance to oxidative stress, has no effect on climbing ability throughout life or on lifespan at 25 °C, but decreases lifespan if flies are transferred at 29 °C (Mockett et al. 2003). Other examples are reported by Iliadi and Boulianne (2010). All these results show that, even if many authors measure lifespan as a surrogate of ageing, other ones make use of various indices of ageing in addition to lifespan. This is possible because flies are amenable to studies of behaviour, resistance to stress, fecundity, learning, and so on, in addition to the classical biochemical measures, such as enzymatic activity, that can be performed in animal models.

These studies show that lifespan cannot be considered as a shorthand of ageing: to apprehend the ageing state of flies it is necessary to observe various traits at various ages and not only lifespan. Could we at least conclude that an increased lifespan, if not always indicative of better health, is not the sign of worse health? Unfortunately, it is not always the case. For instance, the effect of various compounds has been tested by the same laboratory in the same short-lived strain (mean lifespan being less than 30 days), by relying on the same procedures. There is thus a good chance that these studies will be able to provide results that can be compared. Lee et al. (2010) supplemented flies with curcumin, an extract from the plant *Curcuma longa*, and observed that it increased the lifespan of males (+16 %) but not of females. Spontaneous locomotor activity was increased in supplemented 1- and 2-week old males but not in older ones, while a slight increase was observed only in the very last surviving 5-week old females. Finally, climbing ability was improved in males (tested at 1 and 5 weeks of age) and only in old females. On the whole, it seems that a lifespan increase is linked with a better healthspan in males, while lifespan and healthspan of females are barely modified: lifespan and healthspan results are in accordance. The same laboratory studied the effect of lamotrigine, an anti-convulsant drug, on lifespan and spontaneous locomotor activity (Avanesian et al. 2010). The drug increased lifespan by 3 days in both sexes (+15 %) and decreased

spontaneous locomotor activity at 1 and 4 weeks of age: lifespan results cannot be used to infer that healthspan is improved. These two studies clearly show that lifespan and healthspan are not different expressions of the same phenotype. It is thus necessary to measure phenotypes linked to health in addition to lifespan to infer conclusions about ageing.

*Lifespan and healthspan in the nematode *Caenorhabditis elegans**

Some decades after *D. melanogaster*, the nematode became a model organism in ageing research when Klass (1983) and Friedman and Johnson (1988) discovered up to twice longer-lived mutants, which are linked to the dauer larval stage (duration in German). In low food conditions, worms can enter this non-feeding stage for up to 2 months before resuming the normal life cycle. This increases the usual 2-3 weeks lifespan at 20 °C in the laboratory (Klass and Hirsh 1976) or the 2 days one in the soil (Van Voorhies et al. 2005).

Observing lifespan of nematodes is straightforward. Worms live in Petri dishes, for only a very few weeks, are easy to feed, and thus most studies of ageing in *C. elegans* report survival curves. However, only a few articles report ageing data and this may be understood because the behaviour of worms is rather poor. It is possible to observe, as a function of age, feeding (e.g. Huang et al. 2004), defecation (Bolanowski et al. 1981), movement (e.g. Duhon and Johnson 1995), habituation of a reflex (Beck and Rankin 1993), or resistance to stress (Cypser and Johnson 2002). Because it is easy to separate movement into 3 classes (Newell Stamper et al. 2018), spontaneous movement (class A), movement only when the worm is touched (B), absence of any movement, close to death (C), “it is generally agreed that assessment of movement is informative” (Ewald et al. 2018) and this is the main behavioural phenotype observed in nematodes. Newell Stamper et al. (2018) showed that long-lived mutants have a longer class B than control worms, the duration of A and C classes being rather similar. It remains that a recent review (Son et al. 2019) reports only a very few results on the relationships between behavioural ageing and lifespan, more active worms being often longer-lived (but see Bolanowski et al. 1981).

Because the available traits to observe ageing in nematodes are not numerous, most authors rely on lifespan but the issue is that wild nematodes live in the soil, and that they cannot escape. This may explain the existence of the dauer larval stage increasing lifespan: because they cannot flee in the event of any threatening stress, such as famine, the best strategy could be to increase lifespan, waiting for better times after entering the dauer larval stage (Le Bourg 2016). Similarly, being unable to flee could explain why nematodes live longer even when subjected to toxic chemicals (juglone +6-29 %: Heidler et al. 2010; plumbagin +12 %: Hunt et al. 2011; 50 ppm hydrogen sulfide +74 %: Miller and Roth 2007). Because escaping is not an option, an appropriate

response could be to increase lifespan, waiting for dilution of the chemical or its destruction in the soil. These effects are probably hormetic, i.e. beneficial effects of a low dose of a toxic product, but one can even hypothesise, because nematodes cannot flee, that doses that are toxic in, say, mammals, are not toxic in worms. Nevertheless, these lifespan increases could also be a real positive effect because worms are given essential molecules (e.g. vitamin E: +22%: Harrington and Harley 1988). Molecules often considered to be beneficial, such as antioxidants (trolox: +31%: Benedetti et al. 2008), could also have a hormetic effect.

Therefore, it could be that an increased lifespan has been selected in nematodes as an appropriate strategy to survive various threats and that toxic and not-toxic compounds could both increase lifespan. If many chemicals could increase lifespan, one could wonder whether observing lifespan in nematodes can be used to infer about results in other species. For example, the 50-ppm hydrogen sulfide dose increasing lifespan in *C. elegans* (Miller and Roth 2007) is the US Occupational Safety and Health Administration peak permissible exposure limit that should never be exceeded, 20 ppm being the limit for a 15 min exposure (Guidotti 2015). Indeed, it could be hypothesised that a longer lifespan in *C. elegans* is not always indicative of better health but, in some cases, of bad living conditions. Observing only lifespan in nematodes can thus be misleading and relying on other phenotypes linked to health is needed.

Lifespan and healthspan in rodents

Rodents are long-lived, expensive to buy and to rear, which implies that recording the lifespan can be an issue and that the sample sizes of lifespan studies are expected to be low when compared to studies with flies or worms. Indeed, if we except a study testing the effect of gamma irradiation with three groups of 300 female mice each, and not a single male (Caratero et al. 1998), other studies do not use so high a number of mice in each group.

Rodents have a large behavioural repertoire, are easy to observe and handle because of their size, and they are mammals. Thus, it is not surprising that experiments on ageing have been done before the two World Wars, for instance, on learning of mice (Yerkes 1909), on exercised and control rats observed throughout life (Slonaker 1912), or on dietary restriction in rats (McCay et al. 1935). Therefore, research on ageing in rodents is very different from that on *C. elegans* and *D. melanogaster*: while studies on these models privilege lifespan rather than ageing, those on rodents focus more on ageing than on lifespan. During the 1970s, Elias and Elias (1976) lamented in a review of the effects of age on learning in rodents that “updated mortality tables for the many inbred strains of rats and mice used in aging research have not been readily available”. It is obviously not to say that biogerontologists were not concerned with the lifespan of rodents, but

simply that observing lifespan in rodents is a challenge because of technical and financial constraints. However, it can be very informative to observe lifespan and ageing of rodents in the same study. For instance, Winter (1998) reported that *Ginkgo biloba* could improve learning and increase lifespan in rats, but only 10 and 20 rats, respectively in the supplemented and control groups, were used for the lifespan experiment. Similarly, Yu et al. (1985) studied the effect of dietary restriction on metabolic and physical traits of rats, on spontaneous locomotor activity throughout life, and on lifespan (40 rats in each lifespan group).

Is it possible to conclude that studies on rodents of both lifespan and ageing are the best choice to infer about human ageing? Unfortunately, the answer is not clearly positive. For instance, while it is known that, like in rodents, being more active is linked with a longer lifespan in humans (review in e.g. Le Bourg 2009), dietary restriction, unlike with many studies in rodents, does not seem to increase lifespan of Rhesus monkeys or mouse lemurs (Le Bourg 2018) and reports that life expectancy was longer in Okinawa than on mainland Japan because of dietary restriction are slightly too enthusiastic (Le Bourg 2012). The contrasting effects of dietary restriction in rodents and monkeys can probably be explained by relying on the life-history strategies of rodents. When confronted with famine, rodents can hardly emigrate, contrarily to migratory birds, elephants, and other large mammals, because of predation and of the limited distance they can cover (Bowman et al. 2002). Thus, it can be understood why a longer lifespan in the event of famine has been selected in rodents: the best strategy is maybe to wait at the same place until food is again available, which can require living longer (Le Bourg 2016). As emphasised by Demetrius (2005), “when it comes to studying ageing and the means to slow it down, mice are not just small humans”.

Because rodents appear not to be the best animal model to study ageing, the obvious conclusion could be that non-human primates offer the best choice.

Lifespan and healthspan in non-human primates

Non-human primates are surely the best animal models to infer conclusions about ageing in human beings. Unfortunately, they can live for several years, as the tiny 70 g mouse lemur *Microcebus murinus*, or decades, as the monkey *Macaca mulatta*. Primates are costly, need large facilities, veterinarians, and also succeeding generations of biogerontologists. Studies of non-human primates are therefore scarce, with low sample sizes, and cannot routinely sacrifice subjects as can be done with flies. It is a pity because, for instance, the brains of 20 % of aged lemurs show lesions similar to those observed in elderly people suffering from Alzheimer’s disease, and lemurs appear to be an appropriate model to study normal and pathological brain ageing (Bons et al. 2006). However, intervention studies could probably not afford to sacrifice many subjects to verify

whether the treatment under study is decreasing, for instance, amyloid plaques. It is useless to say that this conclusion also applies to rhesus monkeys that live much longer.

However, as in the case of mice, one cannot assert that mouse lemurs are like small humans. They give birth to two offspring thrice a year after a 60 days gestation and their lifespan can fit to the length of the photoperiod. Their lifespan is indeed plastic: mean lifespan is 3.8 years under a short “year” (3 months with 8 h light/day and 5 months with 14 h light/day) and 5.3 years under a “normal” year (natural light at the 48.7 N latitude, near Paris, France; Perret 1997). In addition, lemurs are not homeotherms: during the winter, their temperature, highly correlated to the ambient temperature, can fall to 10 °C, they enter a daily torpor (Schmid 2000), and they increase their weight by ca 50 % at the beginning of the cold season (Génin and Perret 2000). To sum up, mouse lemurs are very different from humans. Therefore, for instance, one cannot exclude that, if a “vaccine” against neurodegeneration (neurofibrillary degeneration, amyloid plaques) were discovered in lemurs, this vaccine would not work in humans.

The solution to this dilemma could be to study ageing and lifespan only in rhesus monkeys that are more similar to humans than lemurs, provided the laboratory can pursue experiments during decades. It is thus not surprising that only a very few studies are done, beginning many years before publication: studies of dietary restriction in macaques begun in the 1980s reported the first lifespan results in the 2000s (e.g. Colman et al. 2009). Clearly speaking, despite being very informative, studies of ageing and lifespan in macaques will remain a tiny part of the studies of ageing in animal models.

Lifespan and healthspan in human beings

Taking into account the previous parts of this chapter, one could be led to conclude that the best animal model to study human ageing is *Homo sapiens*. However, many technical and ethical reasons make that studies on human beings, while highly useful for obvious reasons, are not easy to perform.

In addition, like for animal models, lifespan cannot be considered as sufficient to infer conclusions about ageing. For instance, it is now well known that life expectancy and disability-free life expectancy can diverge: life expectancy can increase while disability-free life expectancy stagnates (e.g. Cambois et al. 2013). Among the European Union, France has one of the highest life expectancies but its disability-free life expectancy is close to the average (Jagger et al. 2008). It is not to say that life expectancy is not an indicator of health, particularly when one compares different countries or the changes in a given country. For instance, by contrast with other developed

nations, there is a severe health issue in the USA: mortality is increasing and life expectancy is stalling (Case and Deaton 2015; Ho and Hendi 2018; Woolf et al. 2018). Today, the USA have the lowest life expectancy of high income countries (Ho and Hendi 2018) and the irony is that Cuba, a small country that cannot be an economic competitor of the USA, has now a life expectancy similar to that of the USA (<https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=CU>).

Disability-free life expectancy can be a better measure of health than life expectancy, particularly for clinicians because, when they know the lifespans of their patients, that simply means that their work is over. In any case, it is useless to convince geriatricians and biogerontologists working with human beings to focus on healthspan and health indicators rather than on lifespan, because this is their daily practice. It is not to say that knowing lifespan is useless, but studying lifespan obviously implies that subjects are already dead and the results could apply only to extinct cohorts and not to living elderly people. For instance, there is an effect of the season of birth on lifespan: people born in Autumn had a higher birthweight and lived longer than those born in Spring. This effect is less important in more recent birth cohorts (1889-1918 vs 1863-1888), probably because mothers of the ancient cohorts “who gave birth in spring and early summer experienced longer periods of inadequate nutrition” (Doblhammer and Vaupel 2001). One may bet that this seasonal effect will no longer be observed in cohorts born, say, in the 1960s in high income countries. These results show, however, that early events, even when they happen *in utero*, can be of the highest importance for life at old age. For instance, a low birthweight can be predictive of cardio-vascular diseases at old age (e.g. Fall 2009; Salam et al. 2014).

Conclusions

Lifespan and healthspan are not synonyms and knowing the lifespan of animals is not always a cue for estimating their physiological state at old age. They can live long with bad or good health and, conversely, a short lifespan can indicate bad health or simply an accidental death. Biogerontologists should thus try to observe both lifespan and indicators of health, whenever it is possible, and not conclude that ageing is delayed when they have simply observed a longer lifespan.

Many animal models have been used in biogerontology but some of them such as rotifers (e.g. Enesco and Verdone-Smith 1980) or *Musca domestica* (e.g. Sohal and Buchan 1981) are no longer used, while new models have appeared such as the short-lived fish *Notobranchius furzeri* (e.g. Cellerino 2009) or the longevous naked mole rat *Heterocephalus glaber* (Lewis and Buffenstein 2016). As emphasised by Cellerino (2009) about *N. furzeri*, “the full potential of this model system for analysis of aging-related phenotypes has yet to be realized”. By contrast, biogerontologists working with *H. glaber* have accumulated many results on the ageing of this

animal model, probably because its very peculiar biology (it is an eusocial mammal, like ants are eusocial insects) is intriguing and its 30-year lifespan, practically, prohibits studying its lifespan, but is an encouragement to study its ageing process. One may hope that future studies, no matter the animal model, will try to study both ageing and lifespan, and will not privilege lifespan only, thereby suggesting that lifespan is a good surrogate of ageing. It is not.

References

- Avanesian A, Khodayari B, Felgner Js, Jafari M (2010) Lamotrigine extends lifespan but compromises health span in *Drosophila melanogaster*. *Biogeront* 11:45-52.
- Bansal A, Zhu LJ, Yen K, Tissenbaum HA (2015) Uncoupling lifespan and healthspan in *Caenorhabditis elegans* longevity mutants. *Proc Natl Acad Sci USA* 112:E277-E286.
- Beck CDO, Rankin CH (1993) Effects of aging on habituation in the nematode *Caenorhabditis elegans*. *Behav Proc* 28:145-164.
- Benedetti MG, Foster AL, Vantipalli MC, White MP, Sampayo JN, Gill MS, Olsen A, Lithgow G (2008) Compounds that confer thermal stress resistance and extended lifespan. *Exp Geront* 43:882-891.
- Bolanowski MA, Russell RL, Jacobson LA (1981) Quantitative measures of aging in the nematode *Caenorhabditis elegans*. I. Population and longitudinal studies of two behavioral parameters. *Mech Ageing Dev* 15:279-295.
- Bons N, Rieger F, Prudhomme D, Fisher A, Krause KH (2006) *Microcebus murinus*: a useful primate model for human cerebral aging and Alzheimer's disease? *Genes Brain Behav* 5:120-130.
- Boorse C (1977) Health as a theoretical concept. *Philosophy Sci* 44:542-573.
- Bowman J, Jaeger AG, Fahrig L (2002) Dispersal distance of mammals is proportional to home range size. *Ecology* 83:2049-2055.
- Briga M, Jimeno B, Verhulst S (2019) Coupling lifespan and aging? The age at onset of body mass decline associates positively with sex-specific lifespan but negatively with environment-specific lifespan. *Exp Geront* 119:111-119.
- Cambois E, Blachier A, Robine JM (2013) Aging and health in France: an unexpected expansion of disability in mid-adulthood over recent years. *Eur J Pub Health* 23:575-581.
- Caratero A, Courtade M, Bonnet L, Planel H, Caratero C (1988) Effect of a continuous gamma irradiation at a very low dose on the life span of mice. *Gerontology* 44:272-276.
- Case A, Deaton A (2015) Rising morbidity and mortality in midlife among white non-hispanic Americans in the 21st century. *Proc Natl Acad Sci USA* 112:15078-15083.
- Cellerino A (2009) Life extension in the short-lived fish *Nothobranchius furzeri*. In: Sell C, Lorenzini A, Brown-Borg HM (eds) *Life-span extension. Single cell organisms to man*. Humana Press, Dordrecht. pp. 157-171.
- Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R (2009) Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 325:201-224.

- Cypser JR and Johnson TE (2002) Multiple stressors in *Caenorhabditis elegans* induce stress hormesis and extended longevity. *J Geront Biol Sci* 57A:B109-B114.
- Demetrius L (2005) Of mice and men. When it comes to studying ageing and the means to slow it down, mice aren't just small humans. *Embo Reports* 6:S39-S44.
- Doblhammer G, Vaupel JW (2001) Lifespan depends on month of birth. *Proc Natl Acad Sci USA* 98:2934-2939.
- Duhon SA Johnson TE (1995) Movement as an index of vitality: comparing wild-type and the *age-1* mutant of *Caenorhabditis elegans*. *J Geront Biol.Sci* 50A:B254-B261.
- Elens A, Wattiaux JM (1971) Age and phototactic reactions of *Drosophila melanogaster*. *Droso Inf Serv* 46:81.
- Elias PK, Elias MF (1976) Effects of age on learning ability. *Contributions from animal literature. Exp Aging Res* 2:165-186.
- Enesco HE, Verdone-Smith C (1980) Alpha-tocopherol increases lifespan in the rotifer *Philodina*. *Exp Geront* 15:335-338.
- Ewald CY, Castillo-Quan JI, Blackwell TK (2018) Untangling longevity, dauer, and healthspan in *Caenorhabditis elegans* Insulin/IGF-1-Signalling. *Gerontology* 64:96-104.
- Fall C (2009) Maternal nutrition: Effects on health in the next generation. *Indian J Med Res* 130:593-599.
- Friedman DB and Johnson TE (1988) Three mutants that extend both mean and maximum lifespan of the nematode, *Caenorhabditis elegans*, define the *age-1* gene. *J Geront Biol Sci* 43:B102-B109.
- Garcia MJ, Teets NM (2019) Cold stress results in sustained locomotor and behavioral deficits in *Drosophila melanogaster*. *J Exp Zool A* 331:192-200.
- Génin F, Perret M (2000) Photoperiod-induced changes in energy balance in gray mouse lemurs. *Physiol Behav* 71:315-321.
- Giroux E (2009) Définir objectivement la santé : une évaluation du concept bio statistique de Boorse à partir de l'épidémiologie moderne (*Objectively defining health: an evaluation of the bio-statistical concept of Boorse based on modern epidemiology*). *Revue Philosoph France Etranger* 134:35-58.
- Grotewiel MS, Martin I, Bhandari P, Cook-Wiens E (2005) Functional senescence in *Drosophila melanogaster*. *Ageing Res Rev* 4:372-397.
- Guidotti TL (2015) Hydrogen sulfide intoxication. In: Lotti M, Bleecker ML (eds) *Handbook of Clinical Neurology, Vol. 131 (3rd series) Occupational Neurology*. Elsevier, Oxford. pp. 111-133.

- Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL (2018) Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *J Amer Med Assoc* 319:1723-1725.
- Harman SM, Blackman MR (2004) Use of growth hormone for prevention or treatment of effects of aging. *J. Geront Biol Sci* 59A:652-658.
- Harrington LA, Harley CB (1988) Effect of vitamin E on lifespan and reproduction in *Caenorhabditis elegans*. *Mech Ageing Dev* 43:71-78.
- Heidler T, Hartwig K, Daniel H, Wenzel U (2010) *Caenorhabditis elegans* lifespan extension caused by treatment with an orally active ros-generator is dependent on *daf-16* and *sir-2.1*. *Biogeront* 11:183-195.
- Ho JY, Hendi AS (2018) Recent trends in life expectancy across high income countries: retrospective observational study. *Brit Med J* 362:k2562.
- Huang C, Xiong C, Kornfeld K (2004) Measurement of age-related changes of physiological processes that predict lifespan of *Caenorhabditis elegans*. *Proc Natl Acad Sci USA* 101:8084-8089.
- Hunt PR, Son TG, Wilson MA, Yu QS, Wood WH, Zhang Y, Becker KG, Greig NH, Mattson MP, Camandola S, Wolkow CA (2011) Extension of lifespan in *C. elegans* by naphthoquinones that act through stress hormesis mechanisms. *Plos One* 6:E21922.
- Iliadi KG, Boulianne GL (2010) Age-related behavioral changes in *Drosophila*. *Ann N Y Acad Sci* 1197:9-18.
- Ishii N, Fujii M, Hartman PS, Tsuda M, Yasuda K, Senoo-Matsuda N, Yanase S, Ayusawa D, Suzuki K (1998) A mutation in succinate-dehydrogenase cytochrome b causes oxidative stress and ageing in nematodes. *Nature* 394:694-697.
- Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, Robine JM, Ehleis Team (2008) Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. *Lancet* 372:2124-2131.
- Jeune B, Robine JM, Young R, Desjardins B, Skytthe A, Vaupel JW (2010) Jeanne Calment and her successors. Biographical notes on the longest living humans. In: Maier H, Gampe J, Jeune B, Robine JM, Vaupel JW (eds.), *Supercentenarians*. Springer, Heidelberg. pp. 285-323.
- Klass MR (1983) A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. *Mech Ageing Dev* 22:279-286.
- Klass MR and Hirsh D (1976) Non-ageing developmental variant of *Caenorhabditis elegans*. *Nature* 260:523-525.
- Kopec S (1928) On the influence of intermittent starvation on the longevity of the imaginal stage of

- Drosophila melanogaster*. Brit J Exp Biol 5:204-211.
- Le Bourg E (1985) A longitudinal study of the effects of age on the patterns of movement in *Drosophila melanogaster*. Biol Behav 10:229-240.
- Le Bourg E (1987) The rate of living theory. Spontaneous locomotor activity, aging and longevity in *Drosophila melanogaster*. Exp Geront 22:359-369.
- Le Bourg E (1988) Non-sexual Behaviour. In: Lints FA, Soliman MH (eds) *Drosophila as a model organism for ageing studies*. Blackie and son Ltd. Glasgow. pp 131-139.
- Le Bourg E (1996) Hypergravity and aging in *Drosophila melanogaster*. 8. Proboscis-extension-response threshold to sucrose. Gerontology 42:235-240.
- Le Bourg E (2004) Effects of aging on learned suppression of photopositive tendencies in *Drosophila melanogaster*. Neurobiol Aging 25:1241-1252.
- Le Bourg E (2007) Hormetic effects of repeated exposures to cold at young age on longevity, aging and resistance to heat or cold shocks in *Drosophila melanogaster*. Biogerontology 8:431-444.
- Le Bourg E (2009) Hormesis, aging, and longevity. Biochim Biophys Acta 1790:1030-1039.
- Le Bourg E (2012) Dietary restriction studies in humans: focusing on obesity, forgetting longevity. Gerontology 58:126-128.
- Le Bourg E (2016) The somatotropic axis may not modulate ageing and longevity in humans. Biogeront 14:421429.
- Le Bourg E (2018) Does calorie restriction in primates increase lifespan? Revisiting studies on macaques (*Macaca mulatta*) and mouse lemurs (*Microcebus murinus*)? BioEssays 40: 1800111.
- Le Bourg E., Lints FA (1992) Hypergravity and ageing in *Drosophila melanogaster*. 4. Climbing activity. Gerontology 38:59-64.
- Le Bourg E, Lints FA, Fresquet N, Bullens P (1993) Review. Hypergravity, aging, and longevity in *Drosophila melanogaster*. Comp Biochem Physiol. A 105:389-396.
- Le Bourg E, Lints FA, Lints CV (1984) Does a relationship exist between spontaneous locomotor activity, fitness and life-span in *Drosophila melanogaster* ? Exp Geront 19:205-210.
- Lee KS, Lee BS, Semnani S, Avanesian A, Um CY, Jeon HJ, Seong KM, Yu K, Min KJ, Jafari M (2010) Curcumin extends life span, improves health span, and modulates the expression of age-associated aging genes in *Drosophila melanogaster*. Rejuven Res 13:561-570.
- Lewis K, Buffenstein R (2016) The naked mole-rat: a resilient rodent model of aging, longevity, and healthspan. In: Kaeberlein MR, Martin GM (eds.), *Handbook of the biology of aging, eighth edition*. Academic Press, London. pp. 181-204.
- Lints FA, Le Bourg E, Lints CV (1984) Spontaneous locomotor activity and life span: a test of the

- rate of living theory in *Drosophila melanogaster*. *Gerontology* 30:376-387.
- Loeb J, Northrop JH (1917) On the influence of food and temperature upon the duration of life. *J Biol Chem* 32:103-121.
- MacCay CM, Crowell MF, Maynard LA (1935) The effect of retarded growth upon the length of life span and upon the ultimate body size. *J Nutr* 10:63-79.
- Miller DL, Roth M. (2007) Hydrogen sulfide increases thermotolerance and lifespan in *Caenorhabditis elegans*. *Proc Natl Acad Sc. USA* 104:20618-20622.
- Miquel J, Lundgren PR, Binnard R (1972) Negative geotaxis and mating behavior in control and gamma-irradiated *Drosophila*. *Droso Inf Serv* 48:60-61.
- Mockett RJ, Bayne ACV, Kwong LK, Orr WC, Sohal RS (2003) Ectopic expression of catalase in *Drosophila* mitochondria increases stress resistance but not longevity. *Free Rad Biol Med* 34:207-217.
- Newell Stamper BL, Cypser JR, Kechris K, Kitzenberg DA, Tedesco PM, Johnson TE (2018) Movement decline across lifespan of *Caenorhabditis elegans* mutants in the insulin/insulin-like signaling pathway. *Aging Cell* 17:e12704
- Pearl R (1928) *The rate of living*. Knopf, London.
- Pearl R, Miner JR, Parker SL (1927) Experimental studies on the duration of life. XI. Density of population and life duration in *Drosophila*. *Amer Nat* 6:289-318.
- Perret M (1997) Change in photoperiodic cycle affects life span in a prosimian primate (*Microcebus murinus*). *J Biol Rhythms* 12:136-145.
- Pison G (2019) Why is French life expectancy increasing more slowly? *Population & Societies*, 564, March.
- Roelfsema F, Veldhuis JD (2016) Growth hormone dynamics in healthy adults are related to age and sex and strongly dependent on body mass index. *Neuroendocrinol* 103:335-344.
- Salam RH, Das JK, Bhutta ZA (2014) Impact of intra-uterine growth restriction on long-term health, *Current Opinion in Clinical Nutrition and Metabolic Care* 17:249-254.
- Schmid J (2000) Daily torpor in the gray mouse lemur (*Microcebus murinus*) in Madagascar: energetic consequences and biological significance. *Oecologia* 123:175-183.
- Service PM, Hutchinson EW, Mackinley MD, Rose MR (1985) Resistance to environmental stress in *Drosophila melanogaster* selected for postponed senescence. *Physiol Zool* 58:380-389.
- Seugé J, Laugé G, Ferradini C, Deysine A (1985) Accelerated aging of the insect *Drosophila melanogaster* by gamma-irradiations of pupae. *Exp Geront* 20:131-139.
- Slonaker JR (1912) The normal activity of the albino rat from birth to natural death, its rate of growth and the duration of life. *J Anim Behav* 2:20-42.

- Sohal RS, Buchan PB (1981) Relationship between physical activity and life span in the adult housefly *Musca domestica*. *ExpGeront* 16:157-162.
- Son HG, Altintas O, Kim EJE, Kwon S, Lee SJV (2019) Age-dependent changes and biomarkers of aging in *Caenorhabditis elegans*. *Aging Cell* 18:e12853.
- Song M, Hu FB, Wu K, Must A, Chan AT, Willett WC, Giovannucci EL (2016) Trajectory of body shape in early and middle life and all cause and cause specific mortality: results from two prospective US cohort studies. *Brit Med J* 353:i2195.
- Van Voorhies WA, Fuchs J, Thomas S (2005) The longevity of *Caenorhabditis elegans* in soil. *Biol Lett* 1:247-249.
- Wigglesworth VB (1949) The utilization of reserve substances in *Drosophila* during flight. *J Exp Biol* 26:150-163.
- Winter JC (1998) The effects of an extract of *Ginkgo biloba* Egb 761 on cognitive behavior and longevity in the rat. *Physiol Behav* 63:425-433.
- Wolf SH, Chapman DA, Buchanich JM, Bobby KJ, Zimmerman EB, Blackburn SM (2018) Changes in midlife death rates across racial and ethnic groups in the United States: systematic analysis of vital statistics. *Brit Med J* 362:k3096.
- Yerkes RM (1909) Modifiability of behavior in its relations to the age and sex of the dancing mouse. *J Comp Neurol Psychol* 19:237-271.
- Yu BP, Masoro EJ, Mc Mahan CA (1985) Nutritional influences on aging of Fischer 344 rats. I. Physical metabolic and longevity characteristics. *J Geront.* 40:657-670.