Accepted for publication in *Biology and Philosophy* (2020)

Defining Aging

Maël Lemoine[1]

Abstract Aging is an elusive property of life, and many important questions about aging depend on its definition. This article proposes to draw a definition from the scientific literature on aging. First, a broad review reveals five features commonly used to define aging: structural damage, functional decline, depletion, typical phenotypic changes or their cause, and increasing probability of death. Anything that can be called 'aging' must present one of these features. Then, although many conditions are not consensual instances of aging, aging is consensually described as a process of loss characterized by a rate and resulting from the counteraction of protective mechanisms against mechanisms that limit lifespan. Beyond such an abstract definition, no one has yet succeeded in defining aging by a specific mechanism of aging because of an explanatory gap between such a mechanism and *lifespan*, a consensual *explanandum* of a theory of aging. By contrast, a sound theoretical definition can be obtained by revisiting the evolutionary theory of aging. Based on this theory, aging evolves thanks to the impossibility that natural selection eliminates late traits that are neutral mainly due to decreasing selective pressure. Yet, the results of physiological research suggest that this theory should be revised to also account for the small number of different aging pathways and for the existence of mechanisms counteracting these pathways, that must, on the contrary, have been selected. A synthetic, but temporary definition of aging can finally be proposed.

Keywords Aging, disease, evolution, death

[1] Univ. Bordeaux, CNRS, ImmunoConcEpT, UMR 5164, F-33000 Bordeaux, France

☞mael.lemoine@u-bordeaux.fr

1. Introduction

Aging seems to be an elusive property of life. It seems to have no particular function and is hardly subject to natural selection. It is often considered to lie at the crossroads of physical and biological explanations. It seems to be both inevitable and to result from accidents. It is even unclear whether it is a universal property of lifeforms, whether it starts during development or much later, when it is healthy or pathological, and whether it can be measured at all. Any attempt to clarify these issues should begin by addressing the question:

(i) What is aging?

Despite the importance of this question for clarifying other related issues, there is no investigation of the concept of aging in the philosophical literature. However, philosophers of medicine have raised the question:

(ii) Is aging a disease?

Unfortunately, their contribution reflects commonsense rather than science. According to common prescientific conceptions, diseases are "unnatural" because they are dysfunctional, whereas aging is both "natural" and dysfunctional. Boorse (1977) reconciled this apparent paradox by arguing that the ailments of age cannot be dysfunctional in a reference class defined by age itself. However, this standpoint is based merely on a preference for the stipulation that 'aging is natural' over the stipulation that 'aging is dysfunctional.' Other philosophers of medicine take the opposite view (Engelhardt 1977; Caplan 1981; De Winter 2015). However, the science of aging (i.e. biogerontology) rarely bothers with this distinction or associated distinctions between "successful aging," "usual aging," "aging associated with diseases," "age-related diseases"(Rowe and Kahn 1987, 1997; Marengoni et al. 2011). Some assume that aging is a disease, others that it is not (Aubert and Lansdorp 2008), and some simply raise the question without answering it (Berlett and Stadtman 1997). The assimilation of age-related diseases to aging itself in evolutionary medicine (Williams and Nesse 1991) is based on the assumption that both entities should have the same explanation, not that they are the same. This distinction is generally unimportant for the scientific matter in hand.

However, a philosophical approach to the definition of aging should be in line with biology, just as recent philosophical approaches to the concept of disease based on evolutionary biology (Matthewson and Griffiths 2017; Alizon and Méthot 2018).[2]

An apparently less verbal, but increasingly important question is:

(iii) Is aging inevitable?

Much of that debate too has actually been largely verbal, based on the assumption that if aging is a disease, then it must also have other characteristics of diseases, such as being treatable, curable in principle, and so on (de Grey et al. 2002). Leaders in the field of the science of aging, such as Cynthia Kenyon, Lenny Guarente, and David Sinclair, explicitly define aging as a target for therapeutic intervention. However, the assumption that aging is an inevitable process of decay ultimately leading to death has long been an implicit criterion for aging in most biogerontological research studies: whatever is inevitable decay, *must be* part of aging, and *vice versa*. It is unclear whether this criterion can just be dropped without creating confusion about what is and is not aging. A more specific question is whether researchers should target more general, non-specific causes, rather than specific causes of disease (Zoncu et al. 2011), a strategy that defines "geroscience" (Kennedy et al. 2014) and suggests that, for instance, treatments such as metformin and rapamycin should be used in a preventive manner in the healthy (for a discussion of the effects of rapamycinin on the healthy, see Johnson, Rabinovitch, and Kaeberlein (2013)).

Philosophers have more frequently addressed questions (ii) and (iii) than question (i). Other, unexplored questions include:

(iv) Do all living beings age? Harman clearly stated that "the phenomenon of aging and death is universal" (Harman 1981). Conversely, many others, since Weismann (1892), have defended the view that only organisms in which there is a distinction between the soma and germline age (for a criticism of this view, see Partridge and Barton (1993)). The situation in plants remains far from clear.

[2] This paper will thus rely heavily on the scientific literature. It follows Carnap's views on explication (or rational reconstruction) as a preliminary work useful for science (Wagner 2012). It is not only descriptive, but also constructive whenever useful, and reflects important uncertainties instead of trying to solve them.

(v) *Can aging be measured?* There are many scales, scores, and indices of aging, but it remains unclear exactly what is measured. Furthermore, the same phenomenon, methylation, for example, can be measured in different ways (Horvath 2013; Hannum et al. 2013).

(vi) *Is aging a phenomenon restricted to the organism level?* It is commonly claimed that organelles, cells, tissues and organs age. Do they? Do colonies, species, or ecosystems age?

(vii) *Do physical objects age in the same way as living beings?* A related, but different question concerns whether aging should be considered a physical or a biological property of living beings.

(viii) *What logical relationships exist between the many theories of aging?* It is difficult to determine whether the various theories are in competition, or simply based on different *explananda*: in particular, are there several aspects, levels, parts or forms of aging?

One of my goals here is to provide the reader with a comprehensive and articulated view of the definitions of aging in biogerontology. The other one is to propose one definition, as specific as science permits, that reflects science rather than commonsense, in its consensus as well as its controversies. Moreover, I propose that the most promising approach is to derive the definition from a physiologically updated version of the theory of the evolution of aging.

To achieve that, the paper is structured as follows. It starts with explicit definitions of aging in the literature. Biogerontologists generally highlight one or several of the following five main features of aging: structural damage, functional decline, depletion, typical phenotypic changes (or their cause), increasing probability of death (or disease). These common notions constitute the starting point for any philosophical analysis of the concept of aging (section 2). Based on them and on additional properties, distinctions can then be made between consensual and controversial cases of aging, and categories of aging properties can be outlined. Aging is a process, characterized by a rate, with typical manifestations; it may be normal or pathological and it is mediated by mechanisms (section 3). That said, none of these mechanisms can in themselves define 'aging,' principally because there is currently a gap in explanation between mechanisms and manifestation of aging. However, one solid result is that a major *explanandum* of a mechanism of aging is *lifespan* (section 4). An entirely different approach

to the definition of aging involves retrieving a formalized definition of aging from the evolutionary theory of aging. I sketch a reconstruction of this theory and draw a definition from it (section 5). However, it is strange that the evolutionary theory of aging currently makes no reference to relevant findings of molecular biology, which, in turn, largely ignores evolutionary biology. Indeed, one of the key unanswered questions in biogerontology is:

(ix) Does the concept of aging differ between physiology and evolutionary biology?

Traditionally, the physiological definition of aging is based on structural decay/functional decline, whereas the evolutionary definition is based on the probability of death/reproduction. I suggest that a theoretical definition of aging based on evolutionary biology principles could be improved by taking into account more general physiological results, including, in particular, the existence of a limited number of different aging mechanisms, and the crucial contribution of mechanisms counteracting aging (section 6). Based on these premises, I finally phrase a definition of aging (section 7).

2. Features traditionally considered to define aging

The inquiry starts with the examination of explicit definitions of aging in the relevant literature. They reflect five views of aging.[3]

Structural damage

In a first batch of definitions, the main feature of aging is considered to be "a build-up of damage"(Kirkwood et al. 2003). Harman, a pioneer in the field and author of the most cited hypothesis relating to aging has, over the last 50 years, consistently defined 'aging' as follows:

> "Aging is the progressive accumulation of diverse, deleterious changes with time that increase the chance of disease and death" (Harman 2006).

This view is echoed by two defenders of a very different hypothesis concerning the genetic regulation of aging:

[3] Most of the references cited in this article are among the most cited in their field (according to Web of Science). This does not necessarily make them the most interesting, but they are arguably the most representative.

> "Ageing is a process of intrinsic deterioration that is reflected at the population level as an increase in the likelihood of death and a decline in the production of offspring" (Partridge and Gems 2002).

Other formulations also seem to be based on the accumulation of damage, albeit less explicitly: "physical emaciation" (Kirkwood 1977), "progressive loss of physiological integrity" (Lopez-Otin et al. 2013), "a degenerative process" (Berlett and Stadtman 1997).

Many similarly worded formulations clearly emphasizing structural damage are less clearly definitional in their context: "a pattern of cumulative damage" (Finkel and Holbrook 2000), "time-dependent accumulation of damage" (Hoeijmakers 2009), "the progressive accrual of ROS-inflicted damage" (Kujoth et al. 2005; ROS = radical oxygen species), "degradative processes" (Cadenas and Davies 2000). When not definitional, such expressions generally express the *cause* of aging rather than aging itself (explicit in Ames et al. 1993 and Kenyon 2010). However, even those based on the same causal hypothesis (here, oxidative stress) do not distinguish with similar degrees of clarity between the cause of the damage, the damage itself (i.e. aging), and the functional impairment resulting from the damage:

> "Aging and the degenerative diseases associated with it are attributed basically to the deleterious side attacks of free radicals on cell constituents and on the connective tissues." (Harman 1956)

Note that this emphasis on structural damage is always, but not exclusively, associated with the oxidative stress hypothesis. In the glycation hypothesis of aging, the changes to the extracellular matrix induced by Maillard products are presented as structural damage (Wolff et al. 1991). In the senescence hypothesis, telomere attrition can also be seen as progressive structural damage that cannot wholly be attributed to oxidative stress (Collado et al. 2007). Many (if not all) hypotheses concerning the cause of aging, conceive it as the wreaking of damage on structures of the organism.

Functional decline

In a different view, components of organisms become less efficient with time. Two leading figures in the field of the evolutionary biology of aging have proposed the following explicit definition of aging:

> "Ageing is usually defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age."(Kirkwood and Austad 2000; similar definition in Kirkwood 2005).

Similar explicit definitions emphasizing functional decline can be found in many papers (e.g. Kirkwood 2005; Lombard et al. 2005; Kregel and Zhang 2007; Bengtson et al. 2008; Aubert and Lansdorp 2008; Zoncu, Efeyan, and Sabatini 2011; Campisi 2013).

Many more, less explicit definitions can also be found. These definitions are not associated with particular hypotheses relating to the causes of aging. Indeed, some authors support the oxidative stress hypothesis, with oxidation supposed to be the main cause of this functional decline (e.g. Ames, Shigenaga, and Hagen 1993; Shigenaga, Hagen, and Ames 1994; Sohal et al. 1994). Others claim that cell senescence is the major cause of functional decline (e.g. Campisi 2013). Another set of authors propose the hypothesis that this functional decline is genetically regulated (e.g. Mostoslavsky et al. 2006; Alcendor et al. 2007), hormonally regulated (e.g. Lamberts, Beld, et Lely 1997), or regulated by autophagy, that is, the removal of components of the cell by regulated degradation (e.g. Cuervo et al. 2005). Some see the progressive exhaustion of repair mechanisms as the main cause of aging, but still define it as a functional decline (Lombard et al. 2005). Some use vaguer terms best interpreted as variations on a theme of functional decline, such as decline in "vitality" (Medawar 1952; Guarente 2000), progressive loss of homeostasis (Sacher 1956; Kirkwood 1977; Rossi, Jamieson, and Weissman 2008), increasing entropy (Kenyon 2001; 2005; 2010), or decreasing "fractal dynamics" (Goldberger et al. 2002). This family of definitions has penetrated into the more developed subfields of brain aging (Burke and Barnes 2006), and cardiovascular aging, for example (Brandes et al. 2005). They raise similar questions as to whether functional decline is a cause of aging, can be considered to constitute aging itself, or is a consequence of aging, through the decline in growth hormone production, for example (Corpas et al. 1993).

Structural damage is one possible cause of the functional decline of a part. Some definitions include both the accumulation of damage and functional decline, without specifying which is cause and which effect (Martin et al. 1996; Wallace 2005).

Depletion

According to this third view, any damage or loss of function could be repaired or compensated indefinitely, provided that some specific reserve did not decrease. This reserve consists of a

fixed stock of materials (e.g. stem cells, oocytes or nephrons) or a limited number of repair/compensation actions (e.g. replication, protein synthesis, or the elimination of damaged proteins (Brunk and Terman 2002)). Aging is defined as a decrease in this reserve, resulting a lack of structural damage repair, and functional decline. One explicit definition of aging in terms of depletion is:

> "Aging is a complex set of phenotypes characterized by reduced repair and/or regeneration of lost or damaged cells."(Krishnamurthty et al. 2004).

An example of an implicit definition of aging in the same terms would be:

> "As organs reserve decreases, so does the ability to restore homeostasis, and eventually even the smallest perturbation prevents homeostasis from being restored."(Fries 1980)

This view is strongly associated with the stem cell hypothesis of aging (Stenderup et al. 2003) and with replicative senescence (Blasco 2005). It can also be associated with the oxidative stress hypothesis, under the notion of "antioxidative defense" (Poeggeler et al. 1993; Sohal et al. 1994; Shigenaga et al. 1994) and it is also consistent with certain aspects of "immunosenescence," i.e. the aging of the immune system, such as the shrinkage of the thymus or the depletion of naïve T cells (Miller 1996). It has been widely used to explain local aging phenomena, such as ovarian aging (Broekmans et al. 2009), not without challenge (Lamberts et al. 1997), and cognitive aging, albeit under the very vague, possibly tautological notion of "cognitive reserve" (Stern 2012).

There is a difference between the *definition* of aging as the depletion of a reserve and an *explanation* of aging by the depletion of a reserve. It is possible to propose this mechanism as an explanation whilst continuing to define aging as the resulting functional decline or accumulation of structural damage. However, it is difficult to maintain this definition when the explanatory model is challenged.

Such explanatory models have, indeed, been challenged for stem cells (Rando 2006; Rossi et al. 2008) or the brain reserve (Morrison and Hof 1997).

Universal changes in phenotype over the course of a lifetime (or their cause)

According to this fourth view, aging is either a typical late-life phenotype (e.g. wrinkles and white hair) stemming from a common underlying process, or this common underlying process itself. This definition is conceptually poor, because it is not characterized by any overarching

property (such as functional decline or structural damage), and is based merely on a collection of observed traits that come with age.

> "Aging is defined when two criteria are met. First, the probability of death at any point in time increases with the age of the organism. (…) Second, characteristic changes in phenotype occur in all individuals over time due to the limiting processes."(Johnson et al. 1999)

Most articles endorsing this view would give an empty definition of aging and associate it with a causal mechanism or a resulting trait of interest:

> "Aging is a ubiquitous complex phenomenon that results from environmental, stochastic, genetic, and epigenetic events in different cell types and tissues and their interactions throughout life. A pervasive feature of aging tissues and most if not all age-related diseases is chronic inflammation." (Franceschi and Campisi 2014; see also Cuervo et al. 2005, which is similar but with autophagy)

Some authors try to list the phenotypic traits of aging (typically in gerontology): very specific traits, such as "inflammaging," i.e. increasing level of inflammation with age in the absence of infections (Ershler and Keller 2000), or, more frequently, global features, such as frailty, which encompasses sarcopenia (i.e. loss of muscular mass), slow motion, fatigue, loss of appetite, and other features differing between studies (Mitnitski et al. 2001; Fried et al. 2001, 2004; Rockwood et al. 2005; Bandeen-Roche et al. 2006; Dent et al. 2016).[4] Some authors would call these phenotypic traits "aging," whereas others would use the term 'aging' to refer to the phenomena underlying these traits (Doherty 2003).

Atherosclerosis provides an interesting illustration of this problem, as it is sometimes defined as aging, sometimes as a normal consequence of aging, and sometimes as an age-related disease (Brandes et al. 2005).

Progressive increase in the probability of death (or disease)

In this last view, what defines aging (or senescence, as evolutionary biologists often call it) is the particular distribution of the probability of death, and sometimes of disease or reproduction, throughout the lifetime of the individuals in a population.

[4] In humans and many mammals. Depending on how it is defined, sarcopenia is not necessarily a universal trait. An interesting discussion of the aging phenotype of *C. elegans* can be found in (Garigan *et al.* 2002).

> "A population [is] said to experience senescence if it exhibits a progressive increase in the age-specific death rate even when the population is maintained under conditions that are ideal for survival"(Kirkwood and Rose 1991).

Kirkwood and Rose also mention fecundity, fertility or fitness, as do others (Partridge and Barton 1993; Partridge and Gems 2002). This definition is frequent in evolutionary biology. The feature can also be found associated with the other four features considered here, generally as an outcome (Harman 1981, 2006; Aubert and Lansdorp 2008), but not always (Sinclair and Guarente 1997, cited above). As an outcome of aging, it is not exclusively associated with evolutionary biology, and may be considered in association with any hypothesis about the cause of aging, such as oxidative stress (Harman 1981), replicative senescence (Aubert and Lansdorp 2008), inflammaging (Franceschi and Campisi 2014), and gene regulation (Johnson et al. 1999; Cuervo et al. 2005).

At least one definition of aging is given in about 50 of the 130 articles reviewed here. However, very few of these papers propose a formal definition of the type "aging *is X"* (X being one of the five features above). Instead, they simply state that "aging *is associated with X*." This non-committal approach has clear advantages – progress without a clear view of what aging is – and drawbacks – confusion which may also come in the way of progress. Furthermore, a given author may propose several features as different definitions in different papers (or even the same paper): Kirkwood (cited several times above) is a striking example. The probable reason for this is that these characteristics are not really five *definitions* of aging, but rather five *defining features* of aging, even if they sometimes present formally as definitions.[5]

To reflect this loose approach to a definition of aging, I propose to take the following condition as insufficient but necessary for something to be defined as aging:

[5] The choice of a defining feature has empirical consequences. For example, sarcopenia can be interpreted in terms of structural decay and measured as a loss of muscular mass, but also in functional terms, as a loss of strength, or even in terms of the muscle mass/strength ratio (Doherty 2003). It can be used as a sign predictive of disability (Guralnik et al. 1995) or even death.

> *Aging is associated with at least one of the following features: structural damage, functional decline, depletion, a progressive increase of the probability of death, or the phenotypic traits typical of old age.*

3. Debatable issues concerning the extension of 'aging'

A systematic investigation of the same literature shows that aging is also commonly described with several general properties which help define its extension: it is a *process*, has a *rate*, *manifestations*, is a *mechanism* with *causes* and *effects*, and is not neutral to the distinction between *healthy* and *pathological*. These properties also explain why cases of aging are consensual or controversial, certain or uncertain.

The process of aging

To begin with, most papers explicitly refer to aging as a *process*. It would be misleading to address the problem of a scientific definition of aging as the *state* of being aged (as supposed by Boorse's notion of a reference class). This process is exclusively seen as a loss (degeneration, damages, ravages, decline, etc.), never as a gain (e.g. maturation). Progressive structural damage, functional decline or depletion, changes associated with an aging phenotype or an increasing probability of death or disease, constitute aging processes. "Aging itself" or "intrinsic aging" must involve at least one of these processes. However, in a rational reconstruction of the concept of aging it is not possible to determine which of these possibilities is the most appropriate.

A second problem is that processes occur in stages, but the stages of aging remain vague in most papers. In particular, the question of when aging starts is problematic. In biogerontology, aging is most often considered to be a midlife stage, as in Harman's description of life as a "phenomenon of growth, decline and death" (Harman 1956). It is rarely considered important to determine whether aging starts during development (Morange 2011). Only biodemographers, that is demographers using tools of evolutionary biology to study aging populations, have investigated the question of whether aging can end, by investigating the existence of a "late-life plateau" characterized by a high, but non-increasing probability of death (Olshansky and Carnes 1997; Olshansky 2010; Robine et al. 2012). These findings are still seldom taken into account by most evolutionary biologists or molecular

biologists. Does this plateau still nevertheless constitute aging? The timing of reproductive senescence is clearly more important to evolutionary biologists. By contrast, molecular biologists mostly focus on the stage occurring roughly between the age of 45 years and death in humans.

Rate of aging

A minority of researchers focus on the uniformity of the rate of aging in individuals of the same species, for instance by investigating the existence of a genetically programmed “aging clock” (a representative of these "theories of programmed aging" is provided by Miller (1999); and a refutation can be found in Austad (2004)). However, most scientists have been struck by the finding that not all individual organisms of the same species reach the same state of structural damage or functional decline over the same amount of time. This is reflected by the widely accepted distinction between biological age and chronological age. However, even if biological aging is the *definiendum*, most studies use chronological age as a proxy. Typically, this difference is highlighted, but then not taken into account (e.g. Yancik 1997). For instance, oncologists almost always define their categories on the basis of chronological age (e.g. Ahuja et al. 1998). Should aging be rationally reconstructed as a function of degradation or as a function of time?

The various processes involved may also not necessarily be synchronic. For example, according to the so-called “frailty paradox,” older women lose muscular strength very early, but may live for a long time in that state, whereas in men, a loss of muscular strength is a good predictive sign for death (Timiras 2007; Christensen 2008; Gordon et al. 2017). Am I more biologically aged when my immune system is less efficient, than when my muscular mass is reduced but my immune system is fine?

It has also been suggested that the process of aging can be *accelerated* or *retarded*, and that it is *regulated* or *modulated* by a certain number of factors. This may explain the variable rate of aging. However, are we talking about the same process when aging is said to be retarded by the knockout of a particular gene or by decreasing calorie intake to 70% the level observed during *ad libitum* feeding?

This focus on the parameters and variables determining the rate of aging leaves open empirical questions concerning the possibility of reducing this rate partially or to zero, or even achieving a negative rate (rejuvenation). Is any such process with a rate that can be null or

negative still aging? Some time ago, there might have been a consensus that irreversibility and inevitability were characteristic of aging.

Manifestations of aging

The phenotype of aging is sometimes, albeit rarely, defined as aging itself. A first key question concerns the parts of the body that age. In humans, hair, skin, muscles, lungs and kidneys age. But does the saliva, the liver or the microbiota age?

A distinction is made between organismal aging (i.e. the aging of the "whole" body) and focal aging (i.e. the aging of part of the body). It is unclear how to assess organismal aging. Should it be determined as some sort of arithmetic mean of the aging of all the component parts of the body? If we focus on the probability of death, then organismal aging should be interpreted as the aging of the most severely affected parts of the body that are essential for survival. Otherwise, it should probably be considered as some kind of averaged progression, but the best way to calculate it has yet to be determined. Focal aging is easier to define, but less representative of aging itself. Besides, can the aging of organs be reduced to the aging of their component tissues or cells? In the field of aging research, most studies focus on the aging of cells, assuming that the rest must follow. However, the aging of the extracellular matrix, a non-cellular component of all tissues, also appears to be an important, potentially partially cell-independent component of the aging process (Ewald et al. 2015).

We then have to consider the question of how best to measure aging. Without such measurements, the existence of a rate of aging could be called into question, together with the results of most scientific studies of aging. At its simplest, the rate of aging can be inferred from longevity, assuming that, when shielded from extrinsic causes of death, longer life is associated with slower aging (the dauer state in *C. elegans* constitutes a special case). Many other measurements of aging have been proposed, including methylation signatures (Horvath 2013; Hannum et al. 2013), the number of senescent cells in a tissue (Krishnamurthty et al. 2004), mutational load (Shigenaga et al. 1994; Martincorena et al. 2018), the level of inflammation (e.g. Franceschi et al. 2017), and a part of the glycome, i.e. roughly the totality of sugars in the organism (Franceschi et al. 2018). Classical genetic and evolutionary studies are instead based on population measurements (e.g. survival rates). Each of these measurements is assumed to be correlated with both chronological age and longevity — once again, the principal proxies for biological aging available — and to express or explain the five

main features of aging. For example, if the amount of structural damage is measured, then the degree of functional decline, depletion, and so on should, logically, follow. However, it would be going too far to assume that aging is actually the phenomenon targeted by any such measurement (see Ferrucci et al. 2005 for a critical reflection about levels of inflammatory markers as a measurement of aging). Of course, it could be argued *a priori* that any assessment of the accuracy of a measurement of aging is dependent on the definition of aging used. But should the definition determine the measurement, or the measurement determine the definition?

Causes, effects and mechanisms of aging

The very least that can be expected from a satisfactory definition of aging for biomedical research is an articulation of the main features of aging by determining cause and effect relationships. The following is a typical definition:

> "Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death." (Lopez-Otin et al. 2013).

"Loss of physiological integrity," which seems to be used here to mean "structural damage," is the main cause and probably also the main manifestation of aging, the other two features being considered effects according to this definition ("leading to"). This definition rules out, for example, impaired functioning causing the progressive loss of integrity, contrary to a number of the findings reported in this review itself. Other hypotheses have also been put forward. A simple example is shown in Figure 1. The three different causal frameworks specify alternative causal relationships in aging. Conceptual analysis is, therefore, practically limited to making a list of the defining features.

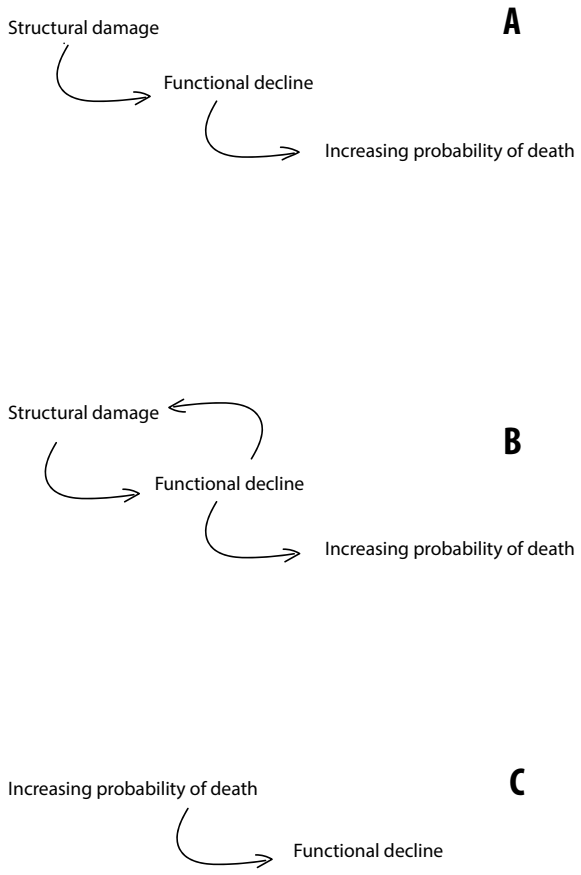

Figure 1. Three different frameworks for causal links between structural damage, functional decline and increasing probability of death. A and B are typical of molecular biology, whereas C is typical of evolutionary biology. Such causal frameworks are compatible with any biological hypothesis about the cause of aging.

A second, independent question concerns what, within such diagrams, should be considered as aging, and what as a cause or effect of aging. If aging is defined as the whole process, then the specified causes and effects constitute its mechanism. If it is one of the nodes of the diagram, then the rest of the diagram corresponds to the causes and effects of aging and the mechanisms of aging are found in the node. The following definition provides a good example of this confusion:

> "Aging is the progressive accumulation of changes at the multicellular level with time that are associated with or responsible for the ever-increasing susceptibility to disease

> and death which accompanies advancing age. These time-related changes are attributed to the aging process." (Harman 1981)

This situation probably reflects a sort of back-tracking process similar to that observed in the investigation of diseases: a disease is first defined as a collection of symptoms, then generally as the underlying imbalance responsible for those symptoms, then as the local deficiency causing the imbalance, and finally based on the etiology of the disease.

The recognition of complex interactions between components of aging often leads scientists to suggest that a vicious circle of some sort is at play (see Medawar (1952) for an example in evolutionary biology; see Kujoth et al. (2005) for an example in molecular biology), or a shift in balance towards greater instability (Ames 1989; Cuervo et al. 2005). Identifying which of these abstract possibilities corresponds to aging would make it possible to develop a more precise definition of aging. For instance, it may be that senescent cells are inflammatory and that inflammation results in the accumulation of even more senescent cells, but that accumulation of damages in mitochondrial DNA does not after all result in even more accumulation of damages in mitochondrial DNA (as proposed by Harman 1972). Here, conceptual clarity depends on empirical progress.

Normal and pathological aging

Pathological aging is sometimes defined as aging with comorbidities ("age-related diseases" such as type 2 diabetes, atherosclerosis, chronic inflammation, neurodegenerative diseases, cancer). It is unclear whether the difference between pathological and normal aging is caused by different courses of aging itself, by different cumulative effects of environmental factors, or different mechanisms (see Finkel and Holbrook (2000) for an alternative view). Other papers define aging without comorbidity and even successful aging as pathological processes. The question as to whether aging is a disease or not clearly cannot be settled by rational argument, given the confusion on this point in this field. Some states, such as cancer and neurodegenerative diseases, clearly cannot be considered to be part of normal aging. The specific case of "premature aging" reflects another source of confusion. Certain diseases, such as progeria, mimic aging. Some experts are happy to describe this as premature or accelerated aging, but others are more cautious and say that these features are "reminiscent of aging," or

"age-like symptoms." It thus remains a matter of debate whether studies of these diseases can teach us anything about aging itself.

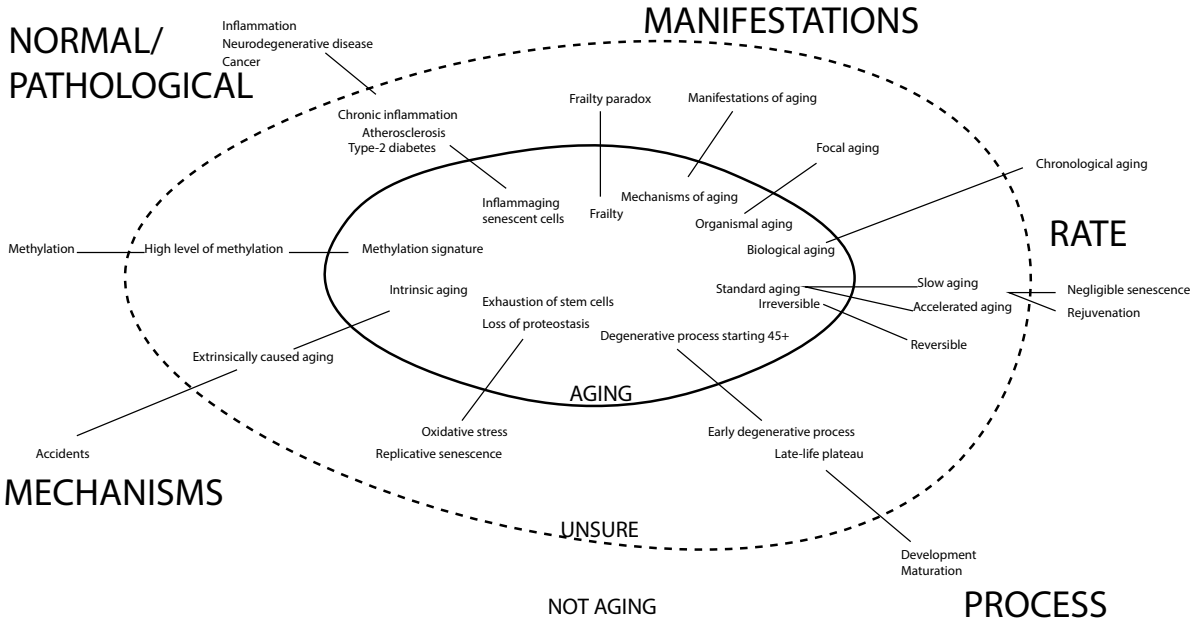

Figure 2. Extension of the concept of aging. The phenomena represented here are either consensual or controversial, certain or uncertain cases of aging. They are ordered by relevant properties investigated in this section.

All the uncertainties presented in this section are summarized in figure 2. Traditional conceptual analysis based on extension of the concept is unlikely to yield any significant definition, given the level of confusion. However, there is minimal consensus about the following condition:

> *Aging is a process characterized by a rate of loss that depends on various mechanisms which either promote or counteract this loss.*

Other properties that are more debatable, such as stages, measurands, causes and effects of aging, and the normality of aging, should be avoided in philosophical reconstructions until such time as biogerontology has made either decisive discoveries or, at least, clearer stipulations.

4. Mechanisms of aging do not define aging

In order to overcome some of these controversies, it might appear a sensible strategy to define aging by a mechanism. For instance, just as water has finally been stipulated to be H_2O with great profit,[6] aging could be defined as a progressive shift in the balance between mitochondrial oxidative damage and the repair of that damage, due to a progressive decline in these repair functions.

However, this approach has not been very successful, mostly due to gaps in explanation. Typically, the first steps in the pathway of aging may be described mechanistically, but the final step may be no more than a correlation with something semantically associated with aging. The most common association is with lifespan, i.e. the ultimate result of any of the processes corresponding to the 5 features above, and the less controversial measurement of aging. For instance, a very successful gene-regulation theory of aging proposed by Kenyon minutely describes interactions between genes (*DAF-2* and *DAF-16*), proteins (sirtuins), receptors (insulin/IGF-1) and interventions (caloric restriction), and then abruptly ends with "long life" (see Kenyon (2005), and figure 3 after Kenyon (2010)). Indeed, which cells are supposed to age like that, with what consequences, and what is the role of other proposed mechanisms?

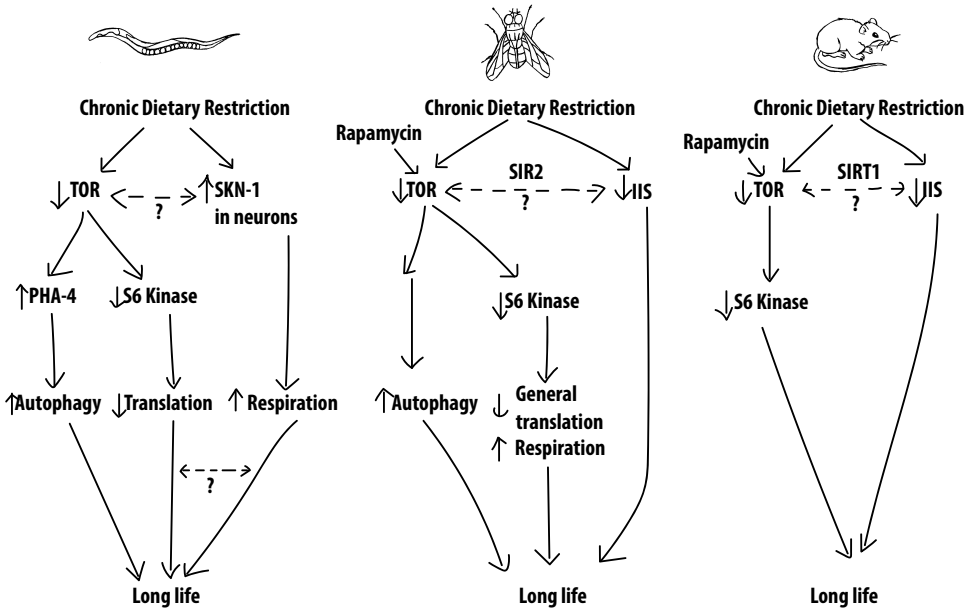

Figure 3. An example of a gap in explanation in aging research (after Kenyon 2010).

[6] Thanks to an anonymous referee for suggesting the analogy.

Most recent "regulation" theories of aging suffer from the same problem of a deficit of downstream detail, no matter how detailed they may be upstream: see, for instance, the network theory of aging and even its more concrete "inflammaging" version, the genomic maintenance theory, or the autophagy theory (Franceschi et al. 2000; Hoeijmakers 2009; Rubinsztein, Marino, and Kroemer 2011). Notoriously, the oxidative stress theory attributes aging to damage caused by the natural activity of mitochondria, but cannot explain exactly how damage to these organelles is supposed to alter the overall functioning of tissues that also benefit from cell renewal and other forms of maintenance. Returning to Kenyon's figures: to determine whether increased lifespan results from a retardation of aging, we need to determine what counts as aging here, i.e. the missing mechanisms between the first and final steps.

This problem is generally described as "merely correlative results." Many papers rely on such correlations between the manifestations of aging and oxidative stress (Balaban, Nemoto, and Finkel 2005; see also the ephemeral proposal of "mitochondrial medicine" in Wallace (2005)), senescence (Collado et al. 2007), a trio of oxidative stress, autophagy and senescence (Brunk and Terman 2002), or a number of other possibilities. Some candidly recognize the problem:

> "There is a risk of tautologies if one starts with the premises that declining stem-cell function is responsible for tissue ageing and that tissue ageing determines longevity. (…) The (…) premise fails to acknowledge the experimental and conceptual gap that exists between our understanding of tissue ageing and the determinants of lifespan. Commonsense dictates that there must be a relationship between the two, and experimental interventions that alter the lifespan of model organisms also tend to alter tissue ageing, but the direct link remains elusive." (Rando 2006)

A rough and ready line of argumentation against a competing causal hypothesis is to denounce the existence of a mere correlation between the championed mechanism of aging and manifestations of aging (striking examples are provided by Bratic and Larsson (2013); Kregel and Zhang (2007); Krtolica et al. (2001); Lombard et al. (2005); Aubert and Lansdorp (2008)). Indeed, the gap in explanation is generally addressed through a correlation with longevity, age-correlated diseases, signs associated with aging such as slow motion or alopecia

(i.e. the loss of hair), or even diseases described as "accelerated aging" (Blasco (2005) defending the replicative senescence theory).

This is as much a semantic as an experimental problem. For example:

> "Time-dependent accumulation of damage in cells and organs is associated with gradual functional decline and aging." (Hoeijmakers 2009)

If aging is defined as the intermediate steps of the process (whatever this may be), then we don't know what aging is. If aging is defined as the outcome of the process, then we haven't really explained how the mechanism produces it. We can get around the first problem by defining these outcomes as aging itself (or as a part of aging). However, to circumvent the problem of a simple correlation rather than an explanation, we tend to define 'aging' as the undescribed intermediate phenomenon generating these outcomes. We may as well stipulate that aging is the *explanans* itself, i.e. the first, described steps of the mechanism that give the theory its name (e.g. oxidative stress theory, stem cell model, mutation theory, genomic instability theory, mitochondrial theory of aging, etc.). Mostly, scientists would not dare define aging as their hypothetical *explanans* of the manifestations of aging. Here is an example showing how arbitrary such a stipulation would sound:

> "aging can be regarded as a process caused by hydroxyl radical pathology and melatonin deficiency." (Poeggeler et al. 1993)

The problem with this definition is that its validation would require colossal amounts of work to demonstrate that *all* manifestations, processes, and proposed mechanisms of aging are caused by this deficiency. Unfortunately, there is no other way around the problem: a final definition requires a definitive theory of aging, even if that theory has multiple components. For this reason, gaps in explanation in aging research necessarily cast doubt on the definitions of aging proposed.

Aging cannot be defined as a mechanism due to lack of a complete picture. Nevertheless, it is useful to define 'mechanisms of aging:'

A necessary condition for a mechanism to be considered a mechanism of aging is that it must be associated, positively of negatively, with the limitation of potential lifespan. [7]

[7] Concepts, such as lifespan and longevity, should nevertheless be clarified as well.

5. The theoretical concept of aging in evolutionary biology

If empirical hypotheses cannot help much, then perhaps it is possible to infer a definition of aging from a theory of aging. Such theories are generally designed to answer explicit questions, such as "why do organisms age?" (Sohal and Weindruch 1996). They rely on an informal, intuitive definition, then formalize their object so that a formalized definition may follow as a byproduct. Such theoretical definitions are abstract and stipulative.[8] However, they are also consistent, potentially quantifiable, explanatory and predictive.

The main theory of aging is a formalization of how aging can possibly evolve by natural selection.[9] In a book that represents the best attempt yet to formalize the whole evolutionary theory of aging, Rose proposed the following theoretical definition:

> "The formal definition of aging to be used here is a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration." (Rose 1995, p. 20).

In this section, I propose a more formalized reconstruction of both the theory and the definition that follows.

The question the theory addresses is: what are the necessary and jointly sufficient conditions for senescence to evolve as a trait? These conditions are:

1) *An age-structured population (Hamilton's condition).* If an 'aged-structured population' meant 'composed of individuals who age,' then the explanation would be circular. An age-structured population is simply a population composed of individuals with traits that differ according to age and have effects on fitness.[10] If individuals simply became indefinitely

[8] Typically, Rose (1995) starts with a definition based on common sense then provides one based on his theory (see below).

[9] An alternative is the reliability theory of aging (Gavrilov and Gavrilova 2001; 2003). Reliability is the probability that a physiological system (organism, organ, etc.) fulfils its role at a given point in its lifetime. This forms the basis of the definition of a mathematical function that represents the accumulation of causes of potential failures of the system. The shape of the resulting curve lies between two extremes: exponential increasing (Gompertz's law of mortality) and exponentially decreasing/increasing (Weibull's law) functions, respectively corresponding to systems with many redundant but less reliable components and to systems with few, non-redundant but extremely reliable components. A simple definition would be: *aging is the progressive disappearance of the parts of a system that make it reliable, according to a pattern lying between Gompertz's law and Weibull's law*. In this view, the diversity of the pathways of aging is lost, but the main feature is probably conserved.

[10] I contrast an age-structured population with an age-structured model of a population. In the former, traits do differ importantly depending on age and not all populations are age-structured, while in the latter, any population can in principle be age-structured, although differing traits are not necessarily important. Hamilton

fitter with age, this would also result in an age-structured population. Species that are not age-structured simply cannot evolve traits like aging. This may be the case for some species with no distinction between germline and soma, and for single-cell organisms reproducing by fission (Austad in Bengtson et al. 2008).

2) *Extrinsic mortality (Medawar's "hazard" condition)*. Extrinsic mortality is all causes of death unrelated to age.[11] A given subset of a population (individuals of age *n*) will necessarily be smaller at a later age (age *n*+*t*) under conditions of extrinsic mortality. As any given generation becomes less populous and, therefore, has fewer offspring with time, hereditary traits that appear only later on (in an age-structured population) are less likely to be selected with increasing age at onset. This, at least, is the classical theory, although it has been challenged repeatedly (Wensink et al. 2017).[12] Given that the theory aims to explain the evolution of aging, the argument would be circular if the age-subset of a population became smaller because of aging. Aging is not necessary but *extrinsic mortality* is.

   > "The force of natural selection weakens with increasing age — even in a theoretically immortal population, provided only that it is exposed to real hazards of mortality." (Medawar 1952)

   Age structure and extrinsic mortality are independent conditions. Indeed, extrinsic mortality does not produce age-structured populations, only populations with smaller age classes as age increases.

3) *Either an accumulation of deleterious traits (Medawar's "dustbin" condition) or antagonistic pleiotropy (Williams' condition).* This third condition is intended to explain how deleterious traits associated with aging can spread in a population. Two explanations have been put forward. First, as deleterious traits appearing later in life are not under

(1966) has described and formalized these effects on a population, but he did not clearly stated that age structure is a condition of the evolution of aging. See also (Charlesworth 1994).

[11] Different definitions of 'extrinsic cause of death' have been used. I consider this one to be the most consistent with the theory of the evolution of aging.

[12] Thanks to an anonymous reviewer for pointing this to me. The reviewer also objected, rightly I think, that if fecundity increases with age, the force of natural selection should not decrease as much (or at all) with age. In this case, this should be added as a condition to the evolution of aging.

strong selective pressure, they are less likely to be selected out and may therefore accumulate in later generations. This is Medawar's "dustbin" condition. Indeed, deleterious traits will accumulate only at the end of life, reinforcing further the effects of extrinsic mortality on selective pressure. The mortality already associated with age structure because of extrinsic mortality is "self-enhanced" because of the existence of "a dustbin for the effects of deleterious genes" (Medawar 1952). This "dustbin" condition also explains why the probability of mortality increases with age, following the so-called "Gompertz curve". Second, traits associated with aging may be associated with favorable effects earlier in life and may be selected for that reason, a phenomenon known as antagonistic pleiotropy. This is Williams' condition. Williams proposed the imaginary example of a gene that strengthen calcification with a positive effect on the bones during growth and a negative effect on arteries later on in life (Williams 1957). Some authors consider these two hypothesis concerning the evolution of aging to be in competition (Partridge and Barton 1993). Others consider them to be merely alternative mechanisms, possibly cumulative, each with limited empirical support (Kirkwood 2005).

4) *Limited maintenance and repair of the soma (Kirkwood's condition)*. Living beings suffer continual damage and must therefore evolve appropriate defense, maintenance and repair mechanisms. More complete maintenance and reparation are associated with a longer potential lifespan and greater fitness. If maintenance and repair are perfect, no aging occurs. Limitations to the maintenance and repair of somatic cells are therefore required for aging to emerge. Such limitations are necessary because of the metabolic trade-off between main functions and maintenance/repair of the soma. The age at onset of senescence is the product of a maximization of fitness. This theory was originally called the error theory (Kirkwood 1977) but was subsequently renamed the "disposable soma theory."

> "The disposable soma theory [is] based on asking how the organism should optimally allocate its metabolic resources, chiefly energy, between the maintenance and repair of its soma and the other functions that it must carry out in order to maximise its Darwinian fitness (…). The necessity for trade-off arises because resources allocated to one function are unavailable to another."(Kirkwood 2005)

The disposable soma theory also explains the modulation of aging (i.e. its advancement or delay, acceleration or slowing) even in genetically homogeneous individuals, in changing environmental conditions (e.g. when food is scarce).[13]

These conditions are combined in the following definition:

Aging is the evolved trait of chronologically decreasing age-specific fitness, necessarily resulting from the accumulation of deleterious traits and/or selection of antagonistic pleiotropic traits during exposure to extrinsic mortality factors in an age-structured population of individuals with necessarily limited repair and maintenance mechanisms.

This theoretical definition of aging, whether phrased in this manner or in a different way, summarizes the most elaborated and cited conception of aging currently available. As such, it should serve as one of the conditions to any representative definition of aging.

6. The physiological facts that should be accounted for in an evolutionary theory

It is certainly possible to argue that the evolutionary theory of aging and the investigation of the mechanisms of aging are just complementary approaches and that each can ignore the other. The evolutionary theory of aging addresses a *why* question and focuses on populations, whereas the physiology of aging answers a *how* question and focuses on individual organisms. For instance, Medawar discussed the pros and cons of populational and individual approaches to the measurement of aging and decided that population approaches were better (Medawar 1952). The evolutionary approach to aging is mostly independent of findings for the molecular and cell biology of aging. Because it is indeed theoretical, it is generally thought as the proper

[13] Slightly different formalized versions of the evolutionary theory of aging can be found in (Rose 1995; Martin et al. 1996; Bengtson et al. 2008). I emphasize logical independence rather than chronological sequence. I also choose to present the main result of the disposable soma theory as an additional, independent condition for aging to evolve. Some think that it is just a case of antagonistic pleiotropy. Kirkwood himself sees them as complementary: while the antagonistic pleiotropy theory explains that variations limiting longevity are selected because they enhance early maintenance, the disposable soma theory explains that variations that limit early maintenance and longevity are selected because they enhance early reproduction (Kirkwood and Rose 1991). In this account, I consider the condition of limited maintenance to be Kirkwood's truly original contribution. An additional question is whether the contribution of biodemography is original (Carey and Vaupel 2006).

framework to define the concept of aging (Rose 1995). As a thought experiment, imagine human skin stretching rather than loosening with age; this would have little or no effect on the evolutionary framework.

However, at least two different general physiological elements call this theory into questions and necessitate greater accuracy: the existence of multiple pathways of aging and the existence of specific counteracting mechanisms for all, or at least most, aging mechanisms.

Multiple mechanisms

The physiological approach to aging has long been dominated by one causal hypothesis: the so-called oxidative stress theory. According to this predominant view, during the normal functioning of the cell, and proportionally to its activity, mitochondria naturally produce large numbers of small, short-lived and highly unstable molecules called radical oxygen species (ROS), which bump into larger, stable molecules, damaging them beyond repair (Miquel et al. 1980; Balaban et al. 2005; Muller et al. 2007). Longstanding stalwarts of this view have straightforwardly attributed the whole process of aging to oxidative damage (Harman 1956, 1972, 1981, 1992, 2006). Accordingly, evolutionary biologists developing this viewpoint, have tended to favor the oxidative stress theory of aging (Rose 1995; Martin et al. 1996).

However, this view is now considered to be indefensible (Muller et al. 2007). Other theories have also been proposed. The replicative senescence theory is based on the progressive shortening of telomeres with each mitosis, until cells enter a so-called senescent state, in which they are no longer able to replicate (Goldstein 1990; Levy et al. 1992; Krtolica et al. 2001; Herker et al. 2004; Collado et al. 2007; Aubert and Lansdorp 2008; Campisi 2013). Other theories focus on DNA damage, or DNA methylation, and the major shifts in cell functioning such changes entail. Others highlight the role of immunosenescence in aging in general (Weksler and Hutteroth 1974; Gillis et al. 1981; Miller 1996; Franceschi et al. 2000; Ershler and Keller 2000; Castle 2000; Renshaw et al. 2002; Gruver et al. 2007).

Some authors have tried to articulate all these pathways into a common, if schematic, mechanism of aging. Mostly, oxidative stress is considered to be the original process, leading on to the other processes. A number of studies have attributed senescence to oxidative stress, either mostly (Campisi 2013) or in part (Krtolica et al. 2001; Lombard et al. 2005). In an even more ambitious review, autophagy, inflammation and senescence were considered to follow on from oxidative stress (Kregel and Zhang 2007).

However, these causal hypotheses are confronted with the problem of gaps in explanation between the corresponding mechanisms and the phenomenon of aging (see section 4). In most studies, these processes are admittedly parallel, cumulative processes that "also contribute to" or "are also associated with" aging. However, each pathway is investigated separately from the others but in correlation with the common *explanandum*: aging (see Kirkwood et al. (2003) for an early recognition of this situation). Many now endorse what could be called the "hallmarks" approach. In this approach, aging is considered to consist of parallel, originally independent but reciprocally enhancing processes: "genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication"(Lopez-Otin *et al.* 2013), or: macromolecular damage, metabolism, stem cells and regeneration, proteostasis, adaptation to stress, inflammation, epigenetics (Kennedy et al. 2014). Unicellular organisms undergo only some of these processes (e.g. oxidative damage), but metazoans also undergo additional pathways of aging (e.g. inflammaging). The theory here is based on a listing of the complete hallmarks and their correct categorization. Consequently, there may be no single physiological concept of aging, given the diversity of the pathways of aging, their mutual independence and their number.

The evolutionary theory of aging is compatible with both the view that there is one mechanism of aging and the view that there are multiple mechanisms of aging. However, Medawar and Williams seem to have had in mind a great number of genetic variations contributing to the same end result. This does not seem to be consistent with the picture of aging that is gradually emerging. How can the evolutionary theory of aging explain the fact of a limited number of mechanisms, and their extension to various taxa?

Some progress has been made with the distinction between "public" and "private" mechanisms of aging (see Partridge and Gems 2002; originally proposed by Martin, Austad, and Johnson 1996). Public mechanisms of aging are those seen in many species. Private mechanisms are those restricted to certain lineages, or even to a group within a species. "Public" and "private" are relative terms. If aging does indeed occur via several pathways, a few of these pathways evolved a long time ago and are widely conserved, whereas other pathways are more recent, much more numerous, and less widespread. At the end of this spectrum lie the various mechanisms underlying age-related diseases, which tend to be more

species-specific (with possible exceptions, such as cancer). This may also suggest a distinction between aging and age-related diseases, with aging more public and displaying traits common to many species, whereas age-related diseases are more private and include intraspecific traits.

As a result:

Aging consists of a limited number of more public mechanisms limiting potential lifespan, whereas age-related diseases may consist of a much large number of more private mechanisms with the same effect.

Counteracting mechanisms

Above, I highlighted the importance of the *rate* of aging, and the possibility of either accelerating or retarding aging. Building on this idea, Lopez-Otin and colleagues proposed a distinction between "primary causes of cellular damage", "compensatory or antagonistic responses to the damage" and "the end result of the previous two groups of hallmarks (…) ultimately responsible for the functional decline associated with aging." (Lopez-Otin et al. 2013). It is, indeed, striking that almost every mechanism of aging has a compensatory, repair or counteracting mechanism. This is not consistent with aging being due to late traits, on which selection could not act. Instead, it suggests that aging is due to deleterious traits that cannot be countered forever. Such counteracting mechanisms would be likely to be subject to selection. Aging is then likely to result from a combination of the two types of mechanism.

By the end of the 1990s, the investigation for, and discovery of "aging genes" had indeed become a problem for the peaceful coexistence of the fields of evolutionary and molecular biology of aging. These two approaches were even initially presented as rival hypotheses on aging, with test cases (Keller and Genoud 1997). Some evolutionary biologists remain convinced that physiologists just don't understand the basic tenets of the evolutionary framework when they investigate a so-called "genetic" program for aging (Martin et al. 1996), or that they hold a medical rather than a biological view of aging (Rose 1995). In response, Ackermann and Pletcher went so far as to claim that the evolutionary framework has become, in its canonical form, a hindrance to the development of the field (see their chapter in Stearns and Koella 2008).

However, a consensual and synthetic view is now emerging. The gene regulation theory of aging does not insist on the existence of a "program of aging," but instead suggests that genes regulate the rate of aging and explain its variability. Most of the regulatory pathways involved in this process are related to metabolism (Sinclair and Guarente 1997; Johnson et al. 1999; Guarente 2000; Kenyon 2001; Partridge and Gems 2002; Garigan et al. 2002; Hsu et al. 2003; Lombard et al. 2005), through the balance between different programmed regimens of cell activity (glucose consumption, autophagy, etc.). Aging can thus be seen as a byproduct of evolution, the modulation of which directly results from natural selection. In some ecological niches, a lower rate of aging results in fitter organisms. Some life-history traits display forms of plasticity that fully qualify as a modulation of aging. The main mechanism involved in this modulation is generally metabolic, very much in line with Kirkwood's disposable soma theory.

Such views have been expressed in many papers by different authors (Johnson et al. 1999; Guarente and Kenyon 2000; Partridge and Gems 2002; Lombard et al. 2005). To reflect these views, I suggest the following condition for a definition:

> *Aging is a widespread, but non-selected default mechanism that limits lifespan, against which selected mechanisms act, by modulating metabolism and through life-history plasticity in adaptation to various environments.*

7. Conclusion: Proposition of a definition of aging

Based on the results of the sections above (summarized in italics), the following definitions can be proposed:

> **Aging of an organism**. *The aging of an organism is a process resulting from the combination of mechanisms limiting its lifespan ("promotive") and mechanisms modulating their effects ("protective"). The balance between the effects of these two types determines the rate of aging.*
>
> **Mechanism of aging.** *A mechanism of aging is a mechanism that fulfills all the following conditions:*
>
> *a) The mechanism must modulate lifespan by varying the rate of an active process continually increasing the probability of death;*

b) It must be associated with either the promotion or prevention of at least one of the following: structural damage, functional decline, depletion, or simply phenotypic traits typical of old age.

c) It must be universally present in the concerned taxon or taxa.

Promotive mechanism of aging. *A promotive mechanism of aging fulfills all the following conditions:*

a) Its effects increase with age;

b) It has not been selected against because they appear at an age when extrinsic factors of death have reduced the size of the corresponding class of the population;

c) It either is deleterious and simply inherited, or has been selected for, but with pleiotropic antagonistic effects at different stages of the life history;

d) Its effects are sufficiently compensated for to optimize reproduction at the expense of longevity.

Protective mechanisms of aging. *A protective mechanism of aging fulfills all the following conditions:*

a) It counteracts the effects of one or several promotive mechanisms;

b) It repairs damage (to a limited extent) or modulate metabolism in response to various environments.

Age-related disease mechanism. *Any mechanism that fulfills conditions (a) and (b) of a mechanism of aging, but fails to fulfill condition (c) is an aged-related disease mechanism. It either fulfills all four conditions of a promotive mechanism of aging or fails to fulfil one of the conditions of a protective mechanism of aging.*

According to these general definitions, aging should be considered to be a binary process, with a progressively shifting balance between degradation (promotive) and compensation (protective) mechanisms. The progressive accumulation of damage due to oxidative stress cannot be called aging, although it may be a mechanism of aging.

Counterintuitive as it may seem, reparation and modulation are now considered to be mechanisms of aging as variation in efficiency may reduce lifespan in some individuals relative to others.

The mechanisms of wrinkles, baldness and menopause, are not mechanisms of aging in themselves, because they do not influence the rate of aging (a), although the underlying mechanisms do (e.g. alteration of the extracellular matrix, exhaustion of stem cells). Maturation is not a mechanism of aging because it is not associated with features listed in (b). If a mechanism does not limit lifespan in all individuals of a taxon, it is not a mechanism of aging, although a part of it may be a mechanism of aging.

I suggest that the classical evolutionary framework applies well only to promotive mechanisms, and not to protective mechanisms, which have almost certainly been subject to selection. I also suggest that this evolutionary framework is at odds with the molecular biology of aging in that it explains that there may be thousands of promotive traits of aging, but not why there is only a handful of mechanisms of aging. However, thousands of variants of protective mechanisms may explain individual differences in the rate of aging. Finally, this framework does not take into account the activity of all mechanisms of aging since the beginning of life. This shortcoming does not call into question the accumulation of deleterious genes or antagonistic pleiotropy, but it should lead to a reformulation of the theory.

Some mechanisms that limit the reduction of lifespan are not mechanisms of aging because they do not counter promotive mechanisms of aging (e.g. defenses against infection), or because they neither repair tissues nor adapt metabolic rate (e.g. failure to reproduce in some species).

The definitions given here are heavily *theoretical*. They are not necessarily valid for all theories that might be proposed or for all facts about aging yet to be discovered. In this sense, they do not take precedence over the science of aging as a *pretheoretical* delimitation of its object that should hold for *any* theory of aging. They are therefore immune to refutation on the basis of prescientific conceptions, but not to further developments in the science of aging. The goal of providing such definitions is modest. It is not to decide whether *x* is aging. Instead, it is to assess the consistency of the science of aging through the coherence of its object, to reveal limitations, to suggest leads in the theoretical approach to aging, and to provide part of the answer to questions ii-ix listed in the introduction.

These definitions are certainly imperfect, but they show that aging is likely to be coherent enough for the science of aging to thrive on much more than misunderstanding, hype and promises.

Acknowledgements

Thanks to the Conceptual Biology and Medicine Group in Bordeaux, and most particularly to Jean-François Moreau, for reading and commenting on earlier versions of the paper. The final version has improved thanks to the objections of one anonymous referee.

References

Ahuja N, Li Q, Mohan AL, et al (1998) Aging and DNA methylation in colorectal mucose and cancer. Cancer Research 58:5489–5494

Alcendor RR, Gao S, Zhai P, et al (2007) Sirt1 regulates aging and resistance to oxidative stress in the heart. Circulation Research 100:1512–1521. https://doi.org/10.1161/01.RES.0000267723.65696.4a

Alizon S, Méthot P-O (2018) Reconciling Pasteur and Darwin to control infectious diseases. PLoS Biol 16:e2003815. https://doi.org/10.1371/journal.pbio.2003815

Ames BN (1989) Endogenous Oxidative DNA Damage, Aging, and Cancer. Free Radical Research Communications 7:121–128. https://doi.org/10.3109/10715768909087933

Ames BN, Shigenaga MK, Hagen TM (1993) Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci U S A 90:7915–7922

Aubert G, Lansdorp PM (2008) Telomeres and aging. Physiological Reviews 88:557–579. https://doi.org/10.1152/physrev.00026.2007

Austad SN (2004) Is aging programed? Aging Cell 3:249–251. https://doi.org/10.1111/j.1474-9728.2004.00112.x

Balaban RS, Nemoto S, Finkel T (2005) Mitochondria, oxidants, and aging. Cell 120:483–495. https://doi.org/10.1016/j.cell.2005.02.001

Bandeen-Roche K, Xue QL, Ferrucci L, et al (2006) Phenotype of frailty: Characterization in the women's health and aging studies. Journals of Gerontology Series a-Biological Sciences and Medical Sciences 61:262–266. https://doi.org/10.1093/gerona/61.3.262

Bengtson VL, Gans D, Putney N, Silverstein M (eds) (2008) Handbook of Theories of Aging, Second Edition, 2 edition. Springer Publishing Company, New York

Berlett BS, Stadtman ER (1997) Protein oxidation in aging, disease, and oxidative stress.

Journal of Biological Chemistry 272:20313–20316. https://doi.org/10.1074/jbc.272.33.20313

Blasco MA (2005) Telomeres and human disease: ageing, cancer and beyond. Nature Reviews Genetics 6:611. https://doi.org/10.1038/nrg1656

Boorse C (1977) Health as a Theoretical Concept. Philosophy of Science 44:542–573

Brandes RP, Fleming I, Busse R (2005) Endothelial aging. Cardiovascular Research 66:286–294. https://doi.org/10.1016/j.cardiores.2004.12.027

Bratic A, Larsson N-G (2013) The role of mitochondria in aging. Journal of Clinical Investigation 123:951–957. https://doi.org/10.1172/JCI64125

Broekmans FJ, Soules MR, Fauser BC (2009) Ovarian Aging: Mechanisms and Clinical Consequences. Endocrine Reviews 30:465–493. https://doi.org/10.1210/er.2009-0006

Brunk UT, Terman A (2002) The mitochondrial-lysosomal axis theory of aging - Accumulation of damaged mitochondria as a result of imperfect autophagocytosis. European Journal of Biochemistry 269:1996–2002. https://doi.org/10.1046/j.1432-1033.2002.02869.x

Burke SN, Barnes CA (2006) Neural plasticity in the ageing brain. Nature Reviews Neuroscience 7:30–40. https://doi.org/10.1038/nrn1809

Cadenas E, Davies KJA (2000) Mitochondrial free radical generation, oxidative stress, and aging. Free Radical Biology and Medicine 29:222–230. https://doi.org/10.1016/S0891-5849(00)00317-8

Campisi J (2013) Aging, Cellular Senescence, and Cancer. Annual Review of Physiology, Vol 75 75:685–705

Caplan AL (1981) The Unnaturalness of Aging: A Sickness unto Death? In: Caplan AL, Engelhardt Jr HT, McCartney JJ (eds) Concepts of Health and Disease: Interdisciplinary Perspectives. Addison-Wesley, Advanced Book Program/World Science Division, pp 725–737

Carey JR, Vaupel JW (2006) Biodemography. In: Handbook of population. Kluwer Academic Publishers, New York, pp 625–658

Castle SC (2000) Clinical relevance of age-related immune dysfunction. Clinical Infectious Diseases 31:578–585. https://doi.org/10.1086/313947

Charlesworth B (1994) Evolution in Age-Structured Populations. Cambridge University Press

Christensen K (2008) Human Biodemography: Some challenges and possibilities. Demographic Research 19:1575–1586. https://doi.org/10.4054/DemRes.2008.19.43

Collado M, Blasco MA, Serrano M (2007) Cellular senescence in cancer and aging. Cell 130:223–233. https://doi.org/10.1016/j.cell.2007.07.003

Corpas E, Harman D, Blackman M (1993) Human Growth-Hormone and Human Aging. Endocrine Reviews 14:20–39. https://doi.org/10.1210/er.14.1.20

Cuervo AM, Bergamini E, Brunk UT, et al (2005) Autophagy and aging - The importance of maintaining "clean" cells. Autophagy 1:131–140. https://doi.org/10.4161/auto.1.3.2017

de Grey ADNJ, Ames BN, Andersen JK, et al (2002) Time to talk SENS: critiquing the immutability of human aging. Ann N Y Acad Sci 959:452–462; discussion 463-465

De Winter G (2015) Aging as Disease. Med Health Care and Philos 18:237–243. https://doi.org/10.1007/s11019-014-9600-y

Dent E, Kowal P, Hoogendijk EO (2016) Frailty measurement in research and clinical practice: A review. European Journal of Internal Medicine 31:3–10. https://doi.org/10.1016/j.ejim.2016.03.007

Doherty TJ (2003) Invited Review: Aging and sarcopenia. Journal of Applied Physiology 95:1717–1727. https://doi.org/10.1152/japplphysiol.00347.2003

Engelhardt HT (1977) Treating aging: Restructuring the human condition. Extending the Human Life Span: Social Policy and Social Ethics, National Science Foundation 35–40

Ershler WB, Keller ET (2000) Age-Associated Increased Interleukin-6 Gene Expression, Late-Life Diseases, and Frailty. Annu Rev Med 51:245–270. https://doi.org/10.1146/annurev.med.51.1.245

Ewald CY, Landis JN, Abate JP, et al (2015) Dauer-independent insulin/IGF-1-signalling implicates collagen remodelling in longevity. Nature 519:97–101. https://doi.org/10.1038/nature14021

Ferrucci L, Corsi A, Lauretani F, et al (2005) The origins of age-related proinflammatory state. Blood 105:2294–2299. https://doi.org/10.1182/blood-2004-07-2599

Finkel T, Holbrook NJ (2000) Oxidants, oxidative stress and the biology of ageing. Nature 408:239–247. https://doi.org/10.1038/35041687

Franceschi C, Bonafe M, Valensin S, et al (2000) Inflamm-aging - An evolutionary perspective on immunosenescence. In: Toussaint O, Osiewacz HD, Lithgow GJ, Brack C (eds) Molecular and Cellular Gerontology. pp 244–254

Franceschi C, Campisi J (2014) Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. Journals of Gerontology Series a-Biological Sciences and Medical Sciences 69:S4–S9. https://doi.org/10.1093/gerona/glu057

Franceschi C, Garagnani P, Morsiani C, et al (2018) The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. Front Med (Lausanne) 5:61. https://doi.org/10.3389/fmed.2018.00061

Franceschi C, Garagnani P, Vitale G, et al (2017) Inflammaging and "Garb-aging." Trends Endocrinol Metab 28:199–212. https://doi.org/10.1016/j.tem.2016.09.005

Fried LP, Ferrucci L, Darer J, et al (2004) Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. J Gerontol A Biol Sci Med Sci 59:M255–M263. https://doi.org/10.1093/gerona/59.3.M255

Fried LP, Tangen CM, Walston J, et al (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146-156

Fries J (1980) Aging, Natural Death, and the Compression of Morbidity. New England Journal of Medicine 303:130–135. https://doi.org/10.1056/NEJM198007173030304

Garigan D, Hsu AL, Fraser AG, et al (2002) Genetic analysis of tissue aging in Caenorhabditis elegans: A role for heat-shock factor and bacterial proliferation. Genetics 161:1101–1112

Gavrilov LA, Gavrilova NS (2001) The reliability theory of aging and longevity. J Theor Biol 213:527–545. https://doi.org/10.1006/jtbi.2001.2430

Gavrilov LA, Gavrilova NS (2003) The quest for a general theory of aging and longevity. Sci Aging Knowledge Environ 2003:RE5

Gillis S, Kozak R, Durante M, Weksler M (1981) Immunological Studies Of Aging - Decreased Production Of And Response To T-Cell Growth-Factor By Lymphocytes From Aged Humans. Journal of Clinical Investigation 67:937–942. https://doi.org/10.1172/JCI110143

Goldberger AL, Amaral L a. N, Hausdorff JM, et al (2002) Fractal dynamics in physiology: Alterations with disease and aging. Proceedings of the National Academy of Sciences of the United States of America 99:2466–2472. https://doi.org/10.1073/pnas.012579499

Goldstein S (1990) Replicative senescence: the human fibroblast comes of age. Science 249:1129–1133. https://doi.org/10.1126/science.2204114

Gordon EH, Peel NM, Samanta M, et al (2017) Sex differences in frailty: A systematic review and meta-analysis. Experimental Gerontology 89:30–40. https://doi.org/10.1016/j.exger.2016.12.021

Gruver A, Hudson L, Sempowski G (2007) Immunosenescence of ageing. J Pathol 211:144–156. https://doi.org/10.1002/path.2104

Guarente L (2000) Sir2 links chromatin silencing, metabolism, and aging. Genes & Development 14:1021–1026

Guarente L, Kenyon C (2000) Genetic pathways that regulate ageing in model organisms. Nature 408:255. https://doi.org/10.1038/35041700

Guralnik JM, Ferrucci L, Simonsick E, et al (1995) Lower-Extremity Function In Persons Over The Age Of 70 Years As A Predictor Of Subsequent Disability. New England Journal of Medicine 332:556–561. https://doi.org/10.1056/NEJM199503023320902

Hamilton WD (1966) The moulding of senescence by natural selection. J Theor Biol 12:12–45

Hannum G, Guinney J, Zhao L, et al (2013) Genome-wide Methylation Profiles Reveal Quantitative Views of Human Aging Rates. Molecular Cell 49:359–367. https://doi.org/10.1016/j.molcel.2012.10.016

Harman D (1981) The Aging Process. Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences 78:7124–7128. https://doi.org/10.1073/pnas.78.11.7124

Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11:298–300

Harman D (2006) Free Radical Theory of Aging: An Update Increasing the Functional Life Span. In: Rattan S, Kristensen P, Clark BFC (eds) Understanding and Modulating Aging. pp 10–21

Harman D (1972) The Biologic Clock: The Mitochondria? Journal of the American Geriatrics Society 20:145–147. https://doi.org/10.1111/j.1532-5415.1972.tb00787.x

Harman D (1992) Free-Radical Theory Of Aging. Mutation Research 275:257–266. https://doi.org/10.1016/0921-8734(92)90030-S

Herker E, Jungwirth H, Lehmann KA, et al (2004) Chronological aging leads to apoptosis in yeast. Journal of Cell Biology 164:501–507. https://doi.org/10.1083/jcb.200310014

Hoeijmakers JHJ (2009) DNA Damage, Aging, and Cancer. New England Journal of Medicine 361:1475–1485. https://doi.org/10.1056/NEJMra0804615

Horvath S (2013) DNA methylation age of human tissues and cell types. Genome Biology 14:R115. https://doi.org/10.1186/gb-2013-14-10-r115

Hsu A-L, Murphy CT, Kenyon C (2003) Regulation of Aging and Age-Related Disease by DAF-16 and Heat-Shock Factor. Science 300:1142–1145. https://doi.org/10.1126/science.1083701

Johnson FB, Sinclair DA, Guarente L (1999) Molecular biology of aging. Cell 96:291–302. https://doi.org/10.1016/S0092-8674(00)80567-X

Johnson SC, Rabinovitch PS, Kaeberlein M (2013) mTOR is a key modulator of ageing and age-related disease. Nature 493:338–345. https://doi.org/10.1038/nature11861

Keller L, Genoud M (1997) Extraordinary lifespans in ants: a test of evolutionary theories of ageing. Nature 389:958–960. https://doi.org/10.1038/40130

Kennedy BK, Berger SL, Brunet A, et al (2014) Geroscience: Linking Aging to Chronic Disease. Cell 159:709–713. https://doi.org/10.1016/j.cell.2014.10.039

Kenyon C (2001) A conserved regulatory system for aging. Cell 105:165–168. https://doi.org/10.1016/S0092-8674(01)00306-3

Kenyon C (2005) The Plasticity of Aging: Insights from Long-Lived Mutants. Cell 120:449–460. https://doi.org/10.1016/j.cell.2005.02.002

Kenyon CJ (2010) The genetics of ageing. Nature 464:504–512. https://doi.org/10.1038/nature08980

Kirkwood T, Rose M (1991) Evolution of Senescence - Late Survival Sacrificed for Reproduction. Philosophical Transactions of the Royal Society B-Biological Sciences 332:15–24. https://doi.org/10.1098/rstb.1991.0028

Kirkwood TB (1977) Evolution of ageing. Nature 270:301–304

Kirkwood TBL (2005) Understanding the odd science of aging. Cell 120:437–447. https://doi.org/10.1016/j.cell.2005.01.027

Kirkwood TBL, Austad SN (2000) Why do we age? Nature 408:233–238. https://doi.org/10.1038/35041682

Kirkwood TBL, Boys RJ, Gillespie CS, et al (2003) Towards an e-biology of ageing: integrating theory and data. Nat Rev Mol Cell Biol 4:243–249. https://doi.org/10.1038/nrm1051

Kregel KC, Zhang HJ (2007) An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. American Journal of Physiology-Regulatory Integrative and Comparative Physiology 292:R18–R36. https://doi.org/10.1152/ajpregu.00327.2006

Krishnamurthty J, Torrice C, Ramsey MR, et al (2004) Ink4a/Arf expression is a biomarker of aging. Journal of Clinical Investigation 114:1299–1307. https://doi.org/10.1172/JCI200422475

Krtolica A, Parrinello S, Lockett S, et al (2001) Senescent fibroblasts promote epithelial cell growth and tumorigenesis: A link between cancer and aging. Proc Natl Acad Sci U S A 98:12072–12077. https://doi.org/10.1073/pnas.211053698

Kujoth GC, Hiona A, Pugh TD, et al (2005) Mitochondrial DNA Mutations, Oxidative Stress, and Apoptosis in Mammalian Aging. Science 309:481–484. https://doi.org/10.1126/science.1112125

Lamberts SWJ, Beld AW van den, Lely A-J van der (1997) The Endocrinology of Aging. Science 278:419–424. https://doi.org/10.1126/science.278.5337.419

Levy M, Allsopp R, Futcher A, et al (1992) Telomere End-Replication Problem And Cell Aging. Journal of Molecular Biology 225:951–960. https://doi.org/10.1016/0022-2836(92)90096-3

Lombard DB, Chua KF, Mostoslavsky R, et al (2005) DNA repair, genome stability, and aging. Cell 120:497–512. https://doi.org/10.1016/j.cell.2005.01.028

Lopez-Otin C, Blasco MA, Partridge L, et al (2013) The Hallmarks of Aging. Cell 153:1194–

1217. https://doi.org/10.1016/j.cell.2013.05.039

Marengoni A, Angleman S, Melis R, et al (2011) Aging with multimorbidity: A systematic review of the literature. Ageing Research Reviews 10:430–439. https://doi.org/10.1016/j.arr.2011.03.003

Martin GM, Austad SN, Johnson TE (1996) Genetic analysis of ageing: Role of oxidative damage and environmental stresses. Nature Genetics 13:25–34. https://doi.org/10.1038/ng0596-25

Martincorena I, Fowler JC, Wabik A, et al (2018) Somatic mutant clones colonize the human esophagus with age. Science eaau3879. https://doi.org/10.1126/science.aau3879

Matthewson J, Griffiths PE (2017) Biological Criteria of Disease: Four Ways of Going Wrong. The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine 42:447–466. https://doi.org/10.1093/jmp/jhx004

Medawar P (1952) An unsolved problem of biology. University College, London

Miller RA (1999) Kleemeier award lecture: are there genes for aging? J Gerontol A Biol Sci Med Sci 54:B297-307

Miller RA (1996) The Aging Immune System: Primer and Prospectus. Science 273:70–74. https://doi.org/10.1126/science.273.5271.70

Miquel J, Economos AC, Fleming J, Johnson JE (1980) Mitochondrial role in cell aging. Experimental Gerontology 15:575–591. https://doi.org/10.1016/0531-5565(80)90010-8

Mitnitski AB, Mogilner AJ, Rockwood K (2001) Accumulation of Deficits as a Proxy Measure of Aging. The Scientific World JOURNAL 1:323–336. https://doi.org/10.1100/tsw.2001.58

Morange M (2011) Development and Aging. Biol Theory 6:59–64. https://doi.org/10.1007/s13752-011-0010-6

Morrison JH, Hof PR (1997) Life and Death of Neurons in the Aging Brain. Science 278:412–419. https://doi.org/10.1126/science.278.5337.412

Mostoslavsky R, Chua KF, Lombard DB, et al (2006) Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. Cell 124:315–329. https://doi.org/10.1016/j.cell.2005.11.044

Muller FL, Lustgarten MS, Jang Y, et al (2007) Trends in oxidative aging theories. Free Radical Biology and Medicine 43:477–503. https://doi.org/10.1016/j.freeradbiomed.2007.03.034

Olshansky SJ (2010) The law of mortality revisited: interspecies comparisons of mortality. J Comp Pathol 142 Suppl 1:S4-9. https://doi.org/10.1016/j.jcpa.2009.10.016

Olshansky SJ, Carnes BA (1997) Ever since Gompertz. Demography 34:1–15

Partridge L, Barton N (1993) Optimality, Mutation and the Evolution of Aging. Nature

362:305–311. https://doi.org/10.1038/362305a0

Partridge L, Gems D (2002) Mechanisms of ageing: public or private? Nat Rev Genet 3:165–175. https://doi.org/10.1038/nrg753

Poeggeler B, Reiter RJ, Tan D-X, et al (1993) Melatonin, hydroxyl radical-mediated oxidative damage, and aging: A hypothesis. Journal of Pineal Research 14:151–168. https://doi.org/10.1111/j.1600-079X.1993.tb00498.x

Rando TA (2006) Stem cells, ageing and the quest for immortality. Nature 441:1080–1086. https://doi.org/10.1038/nature04958

Renshaw M, Rockwell J, Engleman C, et al (2002) Cutting edge: Impaired toll-like receptor expression and function in aging. Journal of Immunology 169:4697–4701. https://doi.org/10.4049/jimmunol.169.9.4697

Robine J-M, Vaupel JW, Jeune B, Allard M (2012) Longevity: To the Limits and Beyond. Springer Science & Business Media

Rockwood K, Song X, MacKnight C, et al (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ 173:489–495. https://doi.org/10.1503/cmaj.050051

Rose MR (1995) Evolutionary Biology of Aging, New Ed. OUP USA, New York

Rossi DJ, Jamieson CHM, Weissman IL (2008) Stems cells and the pathways to aging and cancer. Cell 132:681–696. https://doi.org/10.1016/j.cell.2008.01.036

Rowe JW, Kahn RL (1987) Human aging: usual and successful. Science 237:143–149. https://doi.org/10.1126/science.3299702

Rowe JW, Kahn RL (1997) Successful aging. Gerontologist 37:433–440. https://doi.org/10.1093/geront/37.4.433

Rubinsztein DC, Marino G, Kroemer G (2011) Autophagy and Aging. Cell 146:682–695. https://doi.org/10.1016/j.cell.2011.07.030

Sacher GA (1956) On the Statistical Nature of Mortality, with Especial Reference to Chronic Radiation Mortality. Radiology 67:250–258. https://doi.org/10.1148/67.2.250

Shigenaga M, Hagen T, Ames B (1994) Oxidative Damage and Mitochondrial Decay in Aging. Proc Natl Acad Sci U S A 91:10771–10778. https://doi.org/10.1073/pnas.91.23.10771

Sinclair DA, Guarente L (1997) Extrachromosomal rDNA circles - A cause of aging in yeast. Cell 91:1033–1042. https://doi.org/10.1016/S0092-8674(00)80493-6

Sohal R, Ku H, Agarwal S, et al (1994) Oxidative Damage, Mitochondrial Oxidant Generation And Antioxidant Defenses During Aging And In Response To Food Restriction In The Mouse. Mechanisms of Ageing and Development 74:121–133. https://doi.org/10.1016/0047-6374(94)90104-X

Sohal RS, Weindruch R (1996) Oxidative Stress, Caloric Restriction, and Aging. Science 273:59–63

Stearns SC, Koella JC (2008) Evolution in Health and Disease, 2nd edn. Oxford University Press, USA, Oxford ; New York

Stenderup K, Justesen J, Clausen C, Kassem M (2003) Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. Bone 33:919–926. https://doi.org/10.1016/j.bone.2003.07.005

Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. The Lancet Neurology 11:1006–1012. https://doi.org/10.1016/S1474-4422(12)70191-6

Timiras PS (ed) (2007) Physiological Basis of Aging and Geriatrics, Fourth Edition, 4 edition. CRC Press, New York

Wagner P (ed) (2012) Carnap's Ideal of Explication and Naturalism. Palgrave Macmillan

Wallace DC (2005) A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: A dawn for evolutionary medicine. Annual Review of Genetics 39:359–407. https://doi.org/10.1146/annurev.genet.39.110304.095751

Weismann A (1892) Essays Upon Heredity and Kindred Biological Problems. Clarendon Press, Oxford

Weksler M, Hutteroth T (1974) Impaired Lymphocyte Function In Aged Humans. Journal of Clinical Investigation 53:99–104. https://doi.org/10.1172/JCI107565

Wensink MJ, Caswell H, Baudisch A (2017) The Rarity of Survival to Old Age Does Not Drive the Evolution of Senescence. Evol Biol 44:5–10. https://doi.org/10.1007/s11692-016-9385-4

Williams G, Nesse R (1991) The Dawn of Darwinian Medicine. Quarterly Review of Biology 66:1–22. https://doi.org/10.1086/417048

Williams GC (1957) Pleiotropy, Natural Selection, and the Evolution of Senescence. Evolution 11:398–411. https://doi.org/10.2307/2406060

Wolff S, Jiang Z, Hunt J (1991) Protein Glycation And Oxidative Stress In Diabetes-Mellitus And Aging. Free Radical Biology and Medicine 10:339–352. https://doi.org/10.1016/0891-5849(91)90040-A

Yancik R (1997) Cancer burden in the aged - An epidemiologic and demographic overview. Cancer 80:1273–1283. https://doi.org/10.1002/(SICI)1097-0142(19971001)80:7<1273::AID-CNCR13>3.3.CO;2-5

Zoncu R, Efeyan A, Sabatini DM (2011) mTOR: from growth signal integration to cancer, diabetes and ageing. Nature Reviews Molecular Cell Biology 12:21–35. https://doi.org/10.1038/nrm3025