Scope and limits of evolutionary theories of aging[1]

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Introduction

Aging is a biological phenomenon that plays a marginal role in evolution. Perhaps for this reason, it has not aroused universal interest among evolutionary biologists. In evolutionary approaches, aging is defined as both a populational and a genetic phenomenon. It is a populational phenomenon, because it can only be observed and measured by the progressive increase in mortality with age in a population. All physiological and individual measurements are, on the contrary, open to question, as Medawar has already noted (Medawar 1952; Medawar 1955). It's a genetic phenomenon, because aging is the intrinsic mortality factor par excellence. In other words, it occurs in senescent species, whatever the environment to which the individuals are subjected. Aging can therefore be conceived as the sum of all late-onset deleterious genetic traits. The combination of these two defining characteristics - populational and genetic phenomena - has led to the explanation of aging as the failure to eliminate deleterious traits due to their late onset in life, i.e., in a period of life when reproductive value is declining and selection pressure is correspondingly decreasing.

The evolutionary approach to aging has an essentially theoretical basis, shaken by a number of controversies. But it also boasts a number of empirical results. Since its origins, it has always been a marginal field in the biological study of aging. It was briefly revived in the 1990s under the name of biodemography. Already drowned out by the relative abundance of work on the cellular and molecular biology of aging, evolutionary theory of aging has been further marginalized in the rise of contemporary biogerontology. Although it has retained official status as a "theoretical framework" for the study of aging, evolutionary theory of aging has itself aged. A few openly question its value, or even denounce its harmfulness. The majority treat it with the indifferent reverence that researchers sometimes show to the opinions of their elders.

How useful is this evolutionary theory of aging to biology and medicine? This chapter first briefly traces the history of the development of this theoretical framework, then attempts to clarify its content and assess its coherence. It then examines the results of this theory. Finally, it diagnoses the causes of the indifference of a field that is nevertheless little organized and unified, that of biogerontology, for the only theoretical framework that claims to have this function.

1] History, players, contributions

The history of the evolutionary theory of aging[2] almost begins with that of the theory of evolution by natural selection itself. It's a marginal biological phenomenon that doesn't

1 In 2016, Michel Morange and I led a reading group at the Centre Cavaillès whose aim was to assess the scientific soundness of "immortalist" theses. Our first session was devoted to reading the Medawar article mentioned in this chapter.

2 Even today, evolutionary biologists sometimes refer to aging as *senescence*, as opposed to *aging*, a practice that was once obligatory. Then, under the influence of molecular biology, it gradually began to be called indifferently *senescence* or *aging*.

explain evolution. It is, however, at least an apparent anomaly that the theory of evolution by natural selection must explain.

Weismann

Apart from a cryptic note by Wallace on the subject (commented by Rose 1995, pp. 4-5), the evolutionary theory of aging was inaugurated by a lecture given in 1881 by August Weismann (Weismann 1892, pp. 1-63). Strictly speaking, this lecture is not about aging, but about lifespan, of which aging is only one factor. More precisely, it's about the way in which a certain lifespan is selected, on a species scale, in the course of evolution. In the first instance, it is selected from below, as natural selection necessarily ensures a "minimum lifespan" or "minimum reproductive time" (Weismann 1892, p. 12-13), which depends essentially on environmental conditions. This part of the lecture, undoubtedly the strongest, has however been overshadowed in most interpretations of Weismann's contribution, focused on aging. There is no evolutionary necessity, Weismann points out, for life to extend beyond this minimum. Nor is it necessary for it to stop at this minimum.

This is the basis of the most criticized argument to which Weismann's contribution has often been reduced, notably under the influence of Medawar's mockery (Medawar 1952). This argument posits that from being merely possible, the reduction in lifespan in the course of evolution becomes not necessary, but useful to the preservation of the species through the elimination of the oldest individuals:

> "It follows, on the one hand, from the necessity of reproduction, and on the other, from the desirability of death, since worn-out individuals have no value for the species, and are even harmful to it, by taking the place of healthy ones. According to the principle of selection, the lives of individuals must therefore have been shortened - assuming they were originally immortal - by the length of time that was of no use to the species"(Weismann 1892, p. 21).

Medawar, who claims to see this as a circular argument, ignores the fact that Weismann distinguishes between irreparable wear and tear due to external accidents - what Medawar himself calls "environmental senescence" - and the intrinsic impossibility of achieving immortality even under favorable environmental conditions - what he calls "innate senescence". Others have suggested that Weismann is sketching out a "group selection" argument (Rose 1995, p. 6). The mechanism envisaged by Weismann is unclear. It does, however, play a fairly marginal role in his proposed theory.

More consequential is the interpretation proposed by Kirkwood in line with his own theory of "disposable soma" (Kirkwood and Cremer 1982). Over time, Weismann would have tended to replace this confused hypothesis of the elimination of worn-out individuals with an explanation in terms of the principle of panmixia - according to which what is not used tends to disappear. The reason would be that any variation unfavorable to the maintenance of a useless trait is useful because it *ipso facto* favors more useful traits in an evolutionary "trade-off". Wear and tear is thus the result of inevitable damage, but also of imperfect repair mechanisms. It is on this fact that the possibility, impossibility or necessity of species aging ultimately rests. According to Weismann, the origin of this imperfection lies in the distinction between the germline and the somatic line (Weismann 1892, p. 26). Whereas the germline must remain immortal for the species to persist, the somatic line is not subject to this requirement. The function of the somatic line is to protect the germline and ensure its perpetuation. This strategy of the living is favorable to the perpetuation of the species, but introduces, according to Weismann, the possibility of death by attrition - its possibility and not its necessity, as Kirkwood's theory implies on the contrary. Weismann seems to consider

that death only becomes necessary when a certain degree of division of labor is achieved beyond the mere germline-soma distinction (Weismann 1892, p. 25).

Medawar

The question from which the illustrious immunologist starts is different: how can a trait as widespread in living organisms as aging be explained by natural selection? Firstly, it's a deleterious trait and not advantageous for reproduction. Secondly, it appears essentially at post-reproductive age, when selection pressure is low. Thirdly, explanations of aging that presuppose the existence of a post-reproductive age overlook the fact that this age itself is part of aging. Fourthly, the selection of an intrinsic form of aging (which Medawar calls "innate senescence") cannot be explained by the prior existence of an extrinsic form of aging (which Medawar calls "environmental senescence"). This is what Weismann's confused explanation seems to presuppose: it would be in the interest of the species for deleterious late traits (innate senescence) to appear, hastening the disappearance of individuals who are already worn out and less efficient (environmental senescence). Medawar would unfairly criticize Weismann for confusing the two forms of aging, or for confusing biological aging with the simple accumulation of time. But he is right to point out that Weismann's explanation presupposes the existence of environmental senescence, when the latter is itself already the effect of innate senescence - an inability to repair the organism completely and perfectly.

What's Medawar's contribution?

The existence of late deleterious traits can only be explained by the absence of elimination of these traits, and not simply by their positive selection: this is Medawar's first presupposition. We shall see that Williams, in particular, challenges this presupposition.

Medawar's second presupposition is that the main characteristic of older individuals is not that they are more worn-out, but that they are less numerous. To dissociate these two characteristics, Medawar resorts to a fascinating thought experiment. In a population of potentially immortal individuals, i.e. those whose vulnerability does not increase with age and whose numbers are renewable - test tubes that can't be worn out but can be broken and replaced immediately - the most advanced age groups would necessarily be the most decimated. If they have exactly the same probability of dying at any age, the same proportion of individuals will disappear at the end of a given time interval, whatever their age - the oldest individuals are then the least numerous because they have played this Russian roulette more often[3] .

These two assumptions lead to a first conclusion. In such a population, selection pressure decreases with age due to extrinsic mortality factors. Indeed, the reproductive value of an age class, i.e. its contribution to population renewal, is proportional to its size. What's more, a late trait cannot be eliminated for effects it has not yet had, but only for effects that are already manifesting themselves. However, late effects, whether deleterious or favorable, can neither be eliminated nor spread through the population by natural selection, because the individuals who suffer or benefit from them are too few in number.

A second conclusion is that if there is neither elimination of a deleterious late trait, nor conservation of a beneficial late trait, there is indeed natural selection of the age of appearance of late traits. The same mutation that cannot be eliminated or conserved by natural

[3] This fundamental point of the theory must be carefully distinguished from Medawar's repeated assertion that aged individuals are rare in nature, which is merely a consequence depending on both what we define as "aged" and what we define as "rare". Nussey and colleagues thus seem to think they are making a decisive argument against Medawar's hypothesis (and in favor of Williams' and Kirkwood's) by highlighting the existence of numerous species in which aged individuals have been observed, whereas one would rather have to show the existence of numerous aged individuals in a senescent species to undermine his hypothesis - and, for that matter, those of Williams and Kirkwood (Nussey et al. 2013). What's more, the authors don't generally give a homogeneous criterion for measuring this physiological senescence.

selection when it manifests its effects late in life, is eliminated or conserved when it manifests them earlier. Each senescent trait is therefore pushed back to an age when selection pressure is too low for natural selection to play a significant role.

It would seem that these senescent traits are very numerous and very heterogeneous: this is Medawar's third presupposition. This presupposition, which is very explicit in Williams' writings, is not explicitly present in Medawar's work, but seems the most plausible in his perspective. There is no reason why deleterious mutations should accumulate around a single "master" mechanism of aging.

It follows from these three combined assumptions that the age at which selection pressure is too low to eliminate a senescence trait is itself a function of two variables: the rate of mortality due to extrinsic factors, and the combined effects of other senescence traits. Three ideas must therefore be taken into account: senescence traits are not selected, their age of appearance is the result of natural selection, and the natural selection of this pivotal age is partly based on the prior existence of senescence traits when such traits are already present. Three major consequences follow from this state of affairs:

1) the appearance of a post-reproductive age - of which the menopause is a radical example - cannot be countered by natural selection if this appearance is sufficiently late and, once established, creates a period of life from which deleterious traits completely escape natural selection, even if the extrinsic mortality rate were to drop considerably and durably enough for the species to evolve.
2) Pleiotropic mutations that appear in a potentially immortal population are unlikely to be eliminated, because "a relatively small advantage conferred early in an individual's life may outweigh a catastrophic disadvantage that only appears later." (Medawar 1952, p. 19-20)
3) in the absence of the menopause phenomenon, we can't eliminate the possibility in principle that a late trait is subject to natural selection. This is only unlikely in practice. The main reason is that senescence is "*self-enhancing*". Indeed, once a sufficient number of senescent traits have appeared, a longevity-enhancing mutation is all the less likely to make a difference, as the other senescent traits will accentuate the slope of population decline after that age. To eliminate senescence by natural selection, not only would extrinsic mortality have to be very low, but all senescence traits would have to be eliminated simultaneously.

Medawar's evolutionary theory of senescence is often presented as a "cumulative theory". This leads to confusion. According to Medawar, the appearance of senescent traits can be explained by an accumulation of non-eliminated traits, not by natural selection. This is the generally accepted view. Partridge and Barton write: "senescence may evolve because of a greater mutational load on the later and less strongly selected part of the life history" (Partridge and Barton 1993). Martin, Austad and Johnson also describe "the passive genomic pile-up of alleles that approach selective neutrality because they have no effect on early-life fitness and deleterious effects only late in life, when selection is weak" (1996). But this is not the whole of Medawar's proposal. In fact, there is natural selection for *the age* at which these traits appear. Their effects are also cumulative, because they tend towards simultaneity, and because this simultaneity reinforces the robustness of the senescence phenomenon. (This characteristic was later called the synchrony of aging traits - see Maynard Smith 1962; Williams 1999). Senescence is therefore not an effect that appears accidentally and could disappear just as accidentally. It is a sum of numerous mutually reinforcing effects which, as they accumulate, make the natural disappearance of any one of them more improbable. This is the sense in which Medawar explains aging as an accumulation of deleterious traits. In this

way, he explains not the phenotype of aging - which is multiple - but its irreversibility at the evolutionary level. Once a species has entered the path of senescence, it is extremely unlikely to emerge - simply because it has entered.

Williams

It could be said that Williams considered Medawar's question resolved in principle. His contribution, however, was more influential than Medawar's on the evolutionary theory of aging.

Williams starts from an equation borrowed from Wright and modified by him. The total effect of a gene on fitness can be represented as the following product:

$$S= (1+m_1p_1)(1+m_2p_2)...(1+m_np_n)$$

where m_i is the magnitude of the effect *i* of the gene in question on reproduction, and p_i the proportion of the probability of reproduction affected by that gene. The probability of survival decreases throughout life independently of aging itself, as Medawar pointed out. The same applies to p_i in relation to any of the late effects of a gene. Even if the negative effect has very large magnitude m_i, it cannot reduce fitness if p_i is very small. In short, this is what Medawar's theory says. However, it says nothing about the other potential effects of the gene in question - that is, it assumes them to be zero or non-existent. The Williams equation therefore generalizes Medawar's theory to all cases where there are several effects, notably at different ages. In particular, it emphasizes the possibility of antagonistic effects of the same gene - a possibility mentioned by Medawar.

What then is the difference with Medawar's hypothesis? Whereas Medawar makes antagonistic pleiotropy a special case of his theory, Williams makes the simple accumulation of late genes with deleterious effects a special case of his. There are two reasons for this.

The first is that Medawar seeks above all to explain how these traits may not be eliminated. That they can be selected for beneficial early effects then appears as a special case. Williams, on the other hand, seeks to explain how these traits can be selected. That they may not be eliminated is, from this point of view, the special case.

The second reason is the low probability, according to Williams, that senescence traits are simply conserved by genetic drift, rather than positively selected. This is made clear by the third postulate of his theory: "it is necessary to postulate genes with opposite effects on fitness at different ages, or more precisely, in different *somatic environments*". Since the existence of antagonistic pleiotropy is a fact, and since some of the opposing effects occur at different ages, this general fact must play a role in aging. It does not follow that this phenomenon plays a major role. But it is the only mechanism that can explain why natural selection plays a positive role in the onset of senescence. There is no justification for this implicit belief in Williams' 1957 article.

Kirkwood

With Kirkwood's contribution, the edifice of evolutionary aging theory can be considered essentially complete.

Proposed in two seminal papers (Kirkwood 1977; Kirkwood and Holliday 1979), *disposable soma theory was* initially developed as a physiological rather than an evolutionary theory of aging. Aging is defined not as a set of traits with late deleterious effects, but as a progressive loss of fidelity in the replication of molecules essential to life. Any living being ages according to the performance and level of activity of its intracellular maintenance and repair system. The level of fidelity of this replication has a cumulative impact and follows a sigmoid curve. In other words, a poorly replicated molecule degrades not only the functioning

of the organism, but also the quality of replication itself. This phenomenon worsens with the level of degradation, and a perfect level of replication is made impossible by stochastic phenomena. This hypothesis aims to explain the exponential mortality curve that characterizes senescence at a populational level.

An organism can allocate its available resources to growth, maintenance and repair, reproduction, storage and defense. But this starting point in no way postulates that resources are limited, only that an allocation is necessary. Even if resources are abundant, one allocation will always be better than another in a given environment (Kirkwood and Rose 1991). In an evolutionary framework, growth and reproduction generally take priority over maintenance and repair, which, beyond a certain limit in time, no longer increase the fitness of the organism due to the weight of extrinsic causes of mortality. "The disposable soma theory asserts that in very general circumstances, the optimal level of investment in maintenance will be less than what would be required for the body to maintain itself indefinitely in the same state." (Kirkwood 2017) Natural selection should therefore tend to select the minimum level of repair necessary to maximize reproduction. In other words, germline propagation trumps somatic lineage maintenance.

The disposable soma theory therefore retains the main assumptions of previous theories, but does not go any further in explaining the selection, or non-elimination, of deleterious traits during evolution. It does, however, shift the focus from degradation mechanisms to the modulation of repair mechanisms. Deleterious traits can be of two kinds, depending on whether they reduce the organism's functional efficiency or its ability to maintain the quality of its molecules. In the latter case, the effect of a mutation that reduces or increases this capacity is major, ubiquitous and reversible by a subsequent mutation in the opposite direction. It is even possible that a resource allocation mechanism is selected, in the form of a mechanism for modulating the organism's investment in maintenance. Kirkwood sees in this possibility

> a primary rhythm impulse system that controls the overall rate of aging and enables a relatively rapid evolution of longevity. If the disposable soma theory is correct, intracellular error regulation mechanisms may turn out to be such a system. It is much easier to understand how natural selection might act to increase the fidelity of macromolecule synthesis than to see how it might suppress a series of more or less synchronized late-acting deleterious genes, any one of which would result in death (Kirkwood and Holliday 1979).

The history of evolutionary aging theory did not end with these three contributions, as we shall see below. However, all subsequent contributions were more technical in nature, and received less attention.

2] Is the evolutionary framework coherent?

Authors who have contributed to the development of evolutionary aging theory have frequently stressed "the importance of a strong and coherent theoretical framework for aging research"(Kirkwood 2005). Yet the three theoretical contributions just reviewed are almost always presented as competing theories. In this section, I summarize the three main theoretical controversies within the evolutionary theory of aging, and then propose a unified presentation of its main contributions.

2.1] Accumulation of mutations or antagonistic pleiotropy?

The first controversy stems from confusion over the relationship between Medawar's "theory of accumulation" and Williams' "theory of antagonistic pleiotropy". Williams himself

is not clear. He simply says that Medawar didn't develop the mechanism of antagonistic pleiotropy, as if his own contribution only concerned a special case, although for him, clearly, the absence of antagonistic pleiotropy is the special case. To this day, some researchers in biogerontology have positioned themselves as if it were ultimately necessary to decide experimentally between the two versions of the evolutionary theory of aging with regard to all the genes involved in aging, on the basis of an examination of how each of them may have arisen - actively selected despite antagonistic pleiotropy or simply neutral, but forming with the others an accumulation of late deleterious effects. Rose sums up the situation well: "This diversity of genetic mechanisms does not, however, place the general theory of the evolution of aging in the slightest difficulty. Any one of them would suffice, and together they suffice, to reveal the evolution of aging. Thus, theoretical evaluation or experimental tests of these alternative genetic mechanisms are not tests of the general theory" (Rose 1995, p. 62). I'll come back to the evidence for both hypotheses below.

Williams also disagrees with Medawar on the question of the number of physiological pathways through which organisms age. In his opinion:

"Fundamental research in gerontology has advanced on the thesis that the aging process will ultimately be elucidated through the discovery of a single physiological process (or a small number of them). Medawar clearly expressed this thesis" (Williams 1957, p. 407).

On the contrary, according to Alan Cohen, mutation accumulation theory "suggests that many mutations make minor contributions to senescence and that these mutations may be more or less independent", which "implies that the mechanisms of aging should be heteroclite, tapping into different aspects of physiological functioning" (Cohen 2018). However, Medawar's most explicit text on this point, to which Williams refers, is much more measured:

> "If we knew of some master factor or *primum movens* in the senescence process - if, for example, every ingredient of degradation depended causally on changes occurring in the pineal gland - then a personal measure of senescence would in principle be entirely adequate. The single master process could be measured, and the rest should follow. But we know of no such master factor; the processes of senescence are engaged, but we don't know which one is at the wheel. All that can be done, therefore, is to record the various manifestations of degradation separately" (Medawar 1955, p. 5).

Rather, it's an agnosticism on the question of a single pathway of aging. In fact, his theory is compatible with both possibilities: a single pathway of aging, or at least a small number of pathways of aging, as well as a large multiplicity of pathways of aging. Nevertheless, Williams considers that the theory of antagonistic pleiotropy predicts the existence of a large number of aging pathways. This question, which has assumed major importance in the most recent developments in biogerontology, is only lightly addressed in this evolutionary framework.

2.2] antagonistic pleiotropy or disposable soma?

It's harder to see the difference between the "theory of antagonistic pleiotropy" and the "theory of disposable soma". Partridge and Barton present them together in the same category of "optimality theories of aging" without explaining what distinguishes them (Partridge and Barton 1993).

The theory of antagonistic pleiotropy and the theory of disposable soma differ firstly in their level of generality. The former covers all forms of combination between an early beneficial effect and a late deleterious effect, while the latter focuses exclusively on combinations between a beneficial effect on *reproduction* and a deleterious effect on

maintenance. They then differ in the way the combination is studied: as a *antagonistic* pleiotropy on the one hand, as an optimal *compromise* on the other. This implies an important difference in the direction of explanation. The theory of antagonistic pleiotropy explains the appearance of the late deleterious effect by the selection of the early beneficial effect. The theory of the disposable soma explains the possibility of the early beneficial effect by mutations unfavorable to maintenance. This, at least, is how Kirkwood and Rose, one a founder of the second theory, the other a proponent of the first, present this difference together (Kirkwood and Rose 1991).

2.3] A vicious circle solved by the disposable soma theory?

Kirkwood already pointed out in his seminal article (Kirkwood 1977) that Medawar's and Williams' theories presuppose a mechanism for "measuring the passage of time" (Kirkwood and Holliday 1979), enabling genes to have different effects at the beginning and end of life. Indeed, at the beginning of his 1957 article, Williams explicitly acknowledges the principle that different "somatic environments" are necessary for the existence of pleiotropic effects. It's also hard to see how Medawar's hypothesis can explain how effects manifest themselves late in life if the organism hasn't already aged.

Certainly, Medawar and Williams may have conceded that the organism changes over time, without these changes necessarily implying functional decline - so it would suffice for the organism to change without necessarily aging, but as soon as aging appears, it is added to the changes the organism undergoes over time. However, Kirkwood seems to rely on his argument to assert the primacy of the compromise logic he defends: genetic variations bring about a compromise between reproduction and maintenance from the very first part of life, responsible for both a certain rate of reproduction and a certain average lifespan. The effects of the same traits do not change over time, because they appear identical at different ages of life, characterized by different somatic environments. It is the traits themselves that produce effects that evolve over time according to a selected level of replicative fidelity. In other words, there is neither survival without maintenance mechanisms, nor perfect maintenance mechanisms. The selection of maintenance mechanisms and a level of maintenance is therefore a necessary condition for the onset of senescence.

2.4] Unification of the evolutionary theory of aging.

Without any internal contradiction to speak of, the evolutionary theory of aging seems heterogeneous if we consider that it consists of one fundamental principle - selection pressure decreases with the age of onset of the effects of a trait - and three possible mechanisms: self-sustained accumulation, antagonistic pleiotropy and optimal compromise. In reality, the core of the theory postulates more than one principle, and its heterogeneity concerns more than just the mechanisms by which senescent traits appear.

The core of the theory, accepted by the three central authors and most of the others, can be broken down as follows:

1. Senescence is a populational property that may arise through the evolution of one or more traits.
2. Senescence can only occur in an age-structured population, i.e. one in which non-neutral traits appear successively over time.
3. Senescence is a set of genetic traits with late-onset deleterious effects.
4. The size of an age class necessarily decreases over time due to extrinsic mortality factors independent of senescence.
5. The later the deleterious effects appear in life history, the less likely they are to be eliminated by natural selection.

Recently, the fourth hypothesis has been called into question (Wensink, Caswell, and Baudisch 2017). In fact, the evolutionary theory of aging does not require an extrinsic mortality factor to reduce the size of an age group for a "selection gradient" to appear. On the contrary, it is sufficient for the proportion of older people in the population to remain constant, i.e. in the minority. This principle has been put forward more recently in the case of unicellular organisms that reproduce by morphologically asymmetrical division (Ackermann et al. 2007).

Beyond this core, there are two additional principles that do not meet with consensus:

6. Senescence implies an initial compromise between the maintenance of the organism and its other functions, notably reproduction, so that the level of maintenance is not maximal, but optimal.
7. Senescence progresses either by a mechanism of antagonistic pleiotropy, or by a self-sustained accumulation of late deleterious effects.

The compromise of condition 6, in which Kirkwood's contribution is acknowledged, is presented as the initial condition for the evolution of the somatic environment (development excepted) and, consequently, an initial mechanism of aging on which all other mechanisms of aging are based. It is not incoherent to oppose this by arguing that the evolution of the somatic environment does not necessarily lead to functional decline. This is a question that can only be answered experimentally. As for the divergence of mechanisms presented in condition 7, it basically holds a fairly minor place in the theory, as Rose pointed out in the quote above.

3] What properties of aging does evolutionary theory explain?

This theory revealed a set of problems to be solved, and as many research programs. They fall into five broad categories.

In the first place, the evolutionary theory of aging explains why and how aging cannot be reduced to a simple physical phenomenon of organism wear and tear. This is a point that has seemed crucial at least since Weismann - although Medawar and Williams criticize him for neglecting it. Some parts of organisms wear out in the physical sense, like teeth (except those of hypsodonts) or insect wings. In most species, at least some parts of organisms repair (or even regenerate) themselves. However, aging does not only concern organisms where no part of the organism repairs itself. In senescent species, on the contrary, even tissues that repair themselves age. Aging is therefore a biological as well as a physical phenomenon: since wear and tear can be compensated for by organisms, explaining senescence means explaining why it is not always compensated for. In other words, we need to explain why evolution has not eliminated physical wear and tear in general, even though it seems likely to reduce *fitness* at least in the majority of cases. This is exactly what the evolutionary theory of aging does. It has led to the study of the limits of regeneration mechanisms rather than wear mechanisms.

Secondly, this theory explains that aging cannot be understood as the effect of a "program", in the sense that evolution selects a development program (Morange 2011). This point has given rise to much confusion and misunderstanding. There is no doubt that genes define an important part of species longevity, in the trivial sense that no individual with the genes of a nematode can have the longevity of a mammal, precisely because of the pattern and rate of aging that characterizes it. However, the aging characteristic of a species has not, strictly speaking, been selected. It results, as it were, from the limits of the set of maintenance traits that have been selected in the course of evolution. A species has not been selected to age from a given age, but to live and reproduce until at least that age - with no genetic guarantee of what happens afterwards. In a way, this is the same difference as between Fordism and certain forms of programmed obsolescence. Designing a vehicle's parts to last for as long as they're needed, and only for as long as they're needed, is not the same thing as equipping the

vehicle with a mechanism that deteriorates these parts once they've lasted for as long as they're needed. In other words, the old organism *may* last longer than necessary, and much of this evolutionarily superfluous duration is determined by the genes. But there are no aging genes in the sense that they have not been selected for this effect (Austad 2004). Some have, however, developed the idea that aging itself could be the object of natural selection (Miller 1999), notably because it would favor evolvability (Goldsmith 2008). These ideas remain very heterodox, however, and have not been widely echoed in the literature. By contrast, as early as 1981, Kirkwod emphasized the articulation of his disposable soma theory with "life history" theories (Kirkwood 1981), stressing the natural selection of trade-offs and optimization that determine entire life trajectories. The study of the role of metabolism-related mechanisms in aging has drawn heavily on these ideas.

Thirdly, the evolutionary theory of aging explains how senescence sets in during the course of evolution, why it is not eliminated once it has taken hold, and why there is no intrinsic acceleration of senescence, but on the contrary, the creation of an equilibrium around an average lifespan largely determined by the extrinsic mortality rate. The greater the environmental pressure, the faster individuals tend to reproduce and age. Conversely, as environmental pressure decreases, a population may favor genes that delay reproduction and eliminate those with later deleterious effects. These ideas suggest a field of study that was fairly well explored at least until the 1990s - how in several model species, mainly Drosophila, the selection of longevity traits, fertility rate, effective longevity and environmental conditions covary (Rose 1995). The following section reviews these results.

Fourthly, the evolutionary theory of aging explains the shape of the mortality curve in any population, as a function of the extrinsic mortality rate and the intrinsic mortality rate. This pattern has been described since the 19th century by Gompertz models (Olshansky and Carnes 1997). The evolutionary theory of aging explains why mortality curves have the shape of a Gompertz curve in senescent species. This type of explanation has given rise to the discipline of biodemography (National Research Council (US) Committee on Population 1997; Carey and Vaupel 2006).

Fifthly, the evolutionary theory of aging gives particular importance to the distinction between germ line and somatic line. Non-senescent species in fact, such as the Hydra, seem unaware of this distinction and can reproduce by budding - somatic cells are germ cells in this species (Schaible et al. 2015). Plants, bacteria, are therefore also interesting cases because the presence or absence of a soma-germen distinction is unclear.

With this problem territory described, it remains to take a closer look at how the evolutionary theory of aging stands up to the test of experimentation.

4] The field of experimental investigation of the evolutionary theory of aging

As early as 1957, Williams deduced 9 consequences that have largely shaped the framework and limits of experimental investigations based on this evolutionary theory of aging:

1) 4 conditions are necessary and sufficient for the evolution of senescence (germ-soma distinction, natural selection, pleiotropic genes, decreasing probability of reproduction with age), of which only the first is not fulfilled by all species. This would therefore be the pivotal characteristic that determines whether a species is senescent or not.
2) The rate of senescence is proportional to the rate of extrinsic mortality during adulthood: predation, access to food, etc., determine the rate at which species age.

3) Species that gain in fecundity after reaching sexual maturity have a lower senescence rate than those that don't gain in fecundity.
4) The rate of senescence differs between the sexes according to differences in the two preceding factors.
5) Senescence strikes several physiological systems at the same time, and not just one earlier than the others. Indeed, if this were the case, natural selection would tend to eliminate the earlier effects of senescence in that system, and postpone its onset.
6) The post-reproductive period for each species is non-existent or very short, except in species impacted by civilization.
7) Senescence begins at the time of reproductive maturation.
8) Rapid individual development is correlated with rapid senescence.
9) The selection of longevity traits in a species reduces vigor traits during youth.

This seemingly vast program was largely, but not entirely, pursued in the decades that followed. Essentially, three major questions were addressed, which Michael Rose summarized in 1994 in chapters 3, 4 and 5 of *Evolutionary Biology of Aging*.

The first question is to establish that there are indeed different genetic effects at different ages of life. Indeed, if the effects of alleles were uniform throughout life, aging would simply be the expression of the limits of natural selection in the shaping of organisms, varying (from one individual to another) and evolving (over time) in exactly the same way as fitness. The longevity of individuals would be a simple function of their fitness and the vagaries of the environment. On the contrary, if the most adapted individuals are not always those who decline the least rapidly, then there may be a specific evolution of aging as a function of the decreasing pressure of natural selection with age. This big question therefore tests the core of the theory as described at the end of section 2 above. On the one hand, it is clear that certain traits increase or decrease both fitness and longevity: Rose takes the example of the *white* allele, which negatively affects the vision of *Drosophila Melanogaster* and impacts both its reproductive capacity and longevity. On the other hand, studies on Drosophila have shown the existence of alleles favoring early reproduction, but not longevity, or vice versa. Most of the evidence is based on experiments to artificially delay reproductive age. This manipulation prolongs the time individuals are exposed to natural selection. Maintained over several generations, it should, according to the evolutionary theory of aging, lead to the emergence of individuals whose aging is delayed. The opposite manipulation - which consists in eliminating individuals early in their reproductive period - should result in the emergence of individuals whose aging is accelerated. Both results have been well established and reproduced in at least two species, *D. melanogaster* and *Tribolium castaneum* (Wattiaux 1968; Rose and Charlesworth 1980; Luckinbill et al. 1984). The same results were obtained in a large study by Stearns on *D. melanogaster* (Stearns et al. 2000). Although these results are generally accepted, their interpretation is disputed. In the aforementioned article, Wensink and colleagues point out that this is because evolutionary theory of aging simply doesn't really imply that harsher extrinsic conditions are necessary for the onset of earlier senescence (Wensink, Caswell, and Baudisch 2017). This point does not prevent these extrinsic conditions from in fact modulating aging, at least in certain species - the cases classically evoked are comparisons between birds and terrestrial animals of the same size, bats and rodents, animals with and without shells, flying and non-flying birds, the former of which have a much greater longevity than the latter, even under favorable conditions. A classic article compares the longevity of solitary insects with that of social insects (Keller and Genoud 1997). However, more recent work has also emphasized that extrinsic mortality factors act, under certain conditions, in an age-differentiated way (reviewed in Furness and Reznick 2017).

The second question is whether aging traits appear through the mechanisms of antagonistic pleiotropy (Williams) or mutation accumulation (Medawar). The two mechanisms are not theoretically exclusive, so the question is rather to establish the existence and frequency of each separately. There are striking examples of antagonistic pleiotropy such as *abnormal abdomen* in *D. mercatorum*. In 2005, Kirkwood acknowledged that well-established examples of antagonistic pleiotropy are rather rare (Kirkwood 2005). In 2013, Nussey and colleagues listed 14 genes that are thought to both increase longevity and reduce fertility or reproductive rate (Nussey et al. 2013: table 1). In humans, work has concluded that there is a positive correlation between Huntington's or hemochromatosis and fertility (Albin 1988). More recently, Judith Campisi has defended the thesis that cellular senescence is a antagonistic pleiotropy mechanism that would have evolved to protect against cancer during the first part of life, but would become carcinogenic in the second half of life due to the pro-inflammatory activity of these cells (Campisi 2013). Some have argued, however, that the advantages and disadvantages of cellular senescence are not necessarily distributed in this way between different ages of life (Giaimo and d'Adda di Fagagna 2012). In the aforementioned Drosophila experiments, females from lines whose reproduction was delayed showed a reduction in early fertility. However, while these examples may establish the existence of antagonistic pleiotropy mechanisms, they fall far short of establishing the frequency of these mechanisms and their importance in the evolution of aging. It's not out of the question that they play only a minor role, as almost every possible pattern is observed, from positive covariation of fitness and longevity, to single-effect alleles involved separately in longevity or early reproduction (Cohen 2020). The accumulation of mutations is another possibility, although it is not possible to assess its frequency: exclusively early breeding experiments have led to the emergence of individuals whose late breeding decreases, while early breeding remains unchanged (Mueller 1987). Moreover, the presence of a antagonistic pleiotropy mechanism simply makes it difficult to detect accumulation (Kirkwood and Rose 1991).

Finally, the third question is to establish whether senescent species are those in which there is a distinction between soma and germ. Measuring senescence (or non-senescence) in different species is tricky. According to the predictions of Williams and Kirkwood, due to the presence or absence of a germen-soma distinction, all vertebrate species should be senescent, all symmetrically dividing unicellulars and multicellulars that reproduce by vegetative fission should be non-senescent. While this is broadly true, there is debate about the senescent nature of some species with a distinct somatic lineage (notably fish and molluscs), while the soma-germen distinction is ambiguous or irrelevant for some species (notably plants). More recently, the debate has focused on the freshwater hydra (*Hydra*), a species that is most likely non-senescent and reproduces either sexually or, more often, by budding. This latter point led Kirkwood to interpret this hydra peculiarity as an indistinction between germline and somatic line (Kirkwood 2005). In reality, the hydra's trunk is indeed made up of three cell types that are both stem cells and functional, but its extremities can be considered to be made up of differentiated and, moreover, "senescent" somatic cells (Boehm et al. 2012). The existence of a germline in Orbicella faveolata, a coral, has reportedly been established (Barfield, Aglyamova, and Matz 2016) - and remains debated (Bythell, Brown, and Kirkwood 2018). Ctenophores are another major exception to this fundamental "law" (Petralia, Mattson, and Yao 2014). It has been fairly widely accepted since Stewart's work that species such as E. coli also exhibit senescence phenomena when prevented from dividing (Stewart et al. 2005). Examination of all these examples, as well as the example of species capable of regeneration, including plathelminths and sponges (Funayama 2010), suggests that *1)* the germen-soma distinction is less important than the stem cell-differentiated distinction pattern, and that *2)*

aging is an earlier and deeper mechanism, which evolution first sought to catch up with through reproduction.

In general, the evolutionary theory of aging has proposed a framework, i.e. a set of predictions around which to focus the hypotheses to be tested experimentally. It is this framework itself that today seems to be cracking under the effect of the diversification of species studied and the sophistication of measurement techniques. In general, Cohen sums up the situation well when he states that all patterns of senescence and non-enescence are found in nature, without simple principles of intelligibility, or simply in line with the basic predictions of the theory, seeming to be respected (Cohen 2018). These difficulties should be an internal source of renewal for evolutionary theories of aging.

5] Everything this theory doesn't talk about

However, the main source of renewal for these theories is probably also fuelling the most serious threat to them: the growing indifference of the molecular and cellular biology of aging towards them. A striking symptom of this indifference is the absence of any mention of the evolution of aging in the most central journal in this field to date (Lopez-Otin et al. 2013), or in a more summary alternative journal, less cited, but co-authored by many important players in this field (Kennedy et al. 2014). One plausible explanation for this situation is the fact that *most of the results obtained by contemporary biogerontology on the mechanisms of aging neither invalidate nor corroborate the evolutionary theory of aging*. Rose noted this as long ago as 1994. These results are simply indifferent, could therefore be valid in a non-evolutionary framework, and therefore do not appear to be constrained by this theory. More radically, some believe that evolutionary theory has been responsible for a focus on evolutionary mechanisms that has kept the most dynamic and promising part of aging studies on the periphery, or even acted as an obstacle to their development (Ackermann and Pletcher 2007).

Another symptom of this hiatus between these two branches of biogerontology could be called the "opportunism" of the evolutionary theory of aging. Whatever the cellular and molecular biology of aging discovers, this theory often seems to manage to interpret it in a way that supports its own positions. In 1996, Martin, Austad and Johnson, three eminent representatives of evolutionary biogerontology, published a review in *Nature* showing that oxidative stress theory, a then central molecular theory of aging, married well with the evolutionary theory of aging (Martin, Austad, and Johnson 1996). This historic theory was then living out its last years of domination of the field, to the point of being considered today as a theory of the past. This "synthesis" article therefore proves to be an almost empty exercise, unable to see the shortcomings of a theory on the verge of death, or to advance a theory that has given most of its contribution.

A third symptom is the powerlessness of evolutionary biologists to give voice when molecular and cellular biologists encroach on their terrain and borrow their conceptual framework without the requisite rigor. A revealing episode is the proposal, mainly under the influence of Judith Campisi, of a "antagonistic pleiotropy" phenomenon to explain the two roles of cellular senescence - on the one hand, a defense mechanism against cancer, on the other, a mechanism that promotes the onset of cancer via proinflammatory activity (Campisi 2013). This very popular hypothesis is very fancifully formulated and probably belied by the facts. Firstly, the theory was formulated to speak of a single trait and its antagonistic, non-contemporary effects - yet cellular senescence and its "inflammatory phenotype" are neither the effects of a single "trait", nor successive in time. Secondly, as cellular senescence plays a role as early as embryogenesis, and this role is not the control of cancerous tissue but the regulation of morphogenesis (Muñoz-Espín et al. 2013; Storer et al. 2013), it cannot have been selected for its protective effect against cancer. Finally, cellular senescence is probably a

label that groups together a set of phenomena that are different from one another. Despite these important reservations, Campisi's theses have become classic to the point of being mentioned in reference textbooks (e.g. in Alberts 2015).

However, it is not a matter of impossibility in principle that evolutionary aging theory should play an important role in a renewed and well-informed biogerontology. For this to happen, at least two conditions must be met. The first is that the evolutionary theory of aging must be prepared not only to question itself, but to transform itself in the face of facts that relate not simply to the senescence or non-senescence of species, or to the presence of a germen-soma distinction, but to the various mechanisms of aging. If it is to provide a framework, as its advocates have always maintained, this framework must be open to revision and, above all, clarification. The second condition is that the evolutionary theory of aging should not hesitate to play a role of refutation, not generally of results, but above all of their extrapolation. An emblematic example is the study of the so-called *nutrient sensing* system. Many of those who have studied this major pathway at the heart of metabolism and proteostasis (Guarente, Kenyon, Sinclair, to name but a few), have proposed very fragile generalizations of results obtained on particular organisms - yeast, C. elegans. The fact that there are genes in these species whose impact on the modulation of lifespan is significant does not, of course, imply that this type of regulation has the same effect on aging in different species. The evolutionary biology of aging has a major role to play here in *1)* proposing a rigorous interpretation of life-history theories to these facts, and specifying the conditions under which these theories apply, and *2)* developing principles for reading the multiplicity of results that are accumulating on the molecular and cellular mechanisms of aging in different species.

7] Conclusion

The evolutionary theory of aging has had an undeniable intellectual appeal, not only because of its conceptual finesse, but also because of its promise to bring aging itself - seemingly the tribute paid by living organisms to their physical nature - back into the fold of phenomena amenable to a biological explanation - evolution. However subtle it may be, it appears limited when it comes to studying the mechanisms of aging, the main obstacle being the excessively wide meshes of this theoretical net, which seems to accommodate all experimental hypotheses.

Today, however, there is a trend towards diversifying the organisms in which to study not just the senescence profile, but the mechanisms of said senescence. This trend calls into question simplistic explanatory schemes such as "since mechanism X contributes to aging in species Y, its presence in species Z must also contribute". Indeed, the most diverse organisms should no longer be studied exclusively because they serve as "models" for the study of aging in humans, or because they present a negligible senescence profile that raises hopes of potential anti-aging treatments. On the contrary, they provide a phylogenetic basis for conjecturing the evolution of a phenomenon - aging - not simply as an accumulation of deleterious traits, or as the selection of antagonistic traits or life histories favorable to fitness, but as a complex interplay of age-promoting and age-protecting mechanisms. The evolutionary theory of aging alone can give coherence and relevance to this enterprise. This is the only way to break away from the naivety of "the mechanism that explains the essential", or from the vagueness of pluralism that seems to prevail today.

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