

To Vladimir Petrovich Skulachev,
father of the concept of phenoptosis,
which is essential to understand aging

Evolutionary Gerontology and Geriatrics

Why and How We Age

Giacinto Libertini^{a,*}, Graziamaria Corbi^{b,c}, Valeria Conti^d,
Olga Shubernetskaya^{e,f}, Nicola Ferrara^{c,g}

Foreword by Alexey Olovnikov^{e,h}

Affiliations:

- ^a Independent researcher, and member of the Italian Society for Evolutionary Biology, Italy;
- ^b Dept. of Medicine and Health Sciences, Univ. of Molise, Campobasso, Italy;
- ^c Italian Society of Gerontology and Geriatrics (SIGG);
- ^d Dept. of Medicine, Surgery and Dentistry, Univ. of Salerno, Baronissi, SA, Italy;
- ^e National medical research center for obstetrics, gynecology and perinatology, Moscow, Russia;
- ^f M.M. Shemyakin–Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia;
- ^g Dept of Translational Medical Sciences, Federico II Univ. of Naples, Naples, Italy;
- ^h Inst. of Biochemical Physics, Russian Academy of Sciences, Moscow, Russia.

Libertini Giacinto, giacinto.libertini@yahoo.com; * corresponding author

Graziamaria Corbi, graziamaria.corbi@unimol.it;

Valeria Conti, vconti@unisa.it;

Olga Shubernetskaya, olgasb21@gmail.com;

Nicola Ferrara, nicola.ferrara@unina.it;

Alexey Olovnikov, olovnikov@gmail.com.

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FOREWORD

The reader receives an important book that sums up the results achieved today by the science of aging and is rich not only in answers but also in questions needing answers. And the authors, performing the role of a collective Virgil, lead the reader through the intricacies of facts and hypotheses, which are abundant in the modern gerontology that rushes to the cherished goal of humanity.

What happens to the body when earthly life has already gone to half? When does aging begin? By chance or not, did it appear in evolution? Is aging only harmful, or has some biological benefit? How and why do the structures and functions of the body change with age? What can give to medicine an understanding of evolutionary processes? Different theories give their answers to such questions. Which of them, and why are closer to the truth?

All this is only a part of the book, it also offers a special view of medicine in general. Authors make a significant contribution to evolutionary medicine, a rapidly growing field, which combines the achievements of evolutionary biology and modern medical science. Following their professional interests, the authors primarily focus on evolutionary gerontology and geriatrics. This research area is interesting for doctors, gerontologists, and all biologists of a wide profile. The new views considered in the book allow a better understanding of the diseases themselves, and at the same time, they help to extract information from medical observations and to use them for further development of evolutionary biology. Noting the existence of numerous mechanisms that are compatible or incompatible with the opposite programmed and non-programmed (stochastic) aging paradigms, the authors develop their own version, namely the so-called “subtelomere-telomere theory” of aging.

The book is beautifully illustrated with graphics, photos, and drawings that enrich the text. Authors use for their aims not only waterfalls of facts, ideas, and conclusions, but even geographical maps. As for geography, it clearly shows the dependence of human health on certain natural parasites that have accompanied our species throughout its long history. Before us is drawn an amazing paradox - the existence of antagonism between the presence of helminths and the development of such dangerous human pathologies as autoimmune and allergic diseases.

In general, I recommend reading this book to physicians, evolutionists, and certainly those who are interested in the problems of aging. And who isn't interested in them now?

Alexey Olovnikov

Terminology + abbreviations (if used more than once)

Hypotheses about aging origin

Aging as an accelerating factor of evolution hypothesis
antagonistic pleiotropy h.
cessation of somatic growth h.
damage accumulation hypotheses
disposable soma h.
historical h.
mutation accumulation h.
quasi-programmed aging h.
Red Queen h.

Diseases

age-related macular degeneration	AMD
Alzheimer's disease	AD
dementia with Lewy bodies	DLB
dyskeratosis congenita	DC
Parkinson's disease	PD
progeroid syndromes	PSs
Werner syndrome or adult progeria	WS

Cell types

endothelial progenitor cells	EPCs
olfactory receptor cells	ORCs
retina pigmented cells	RPCs

Enzymes and molecules

extrachromosomal ribosomal DNA circles	ERCs
mammalian TOR	mTOR
reactive oxygen species	ROS
human TER	hTER
human TERT	hTERT
target of rapamycin	TOR
Telomerase RNA	TER
Telomerase Reverse Transcriptase	TERT
Telomeric Repeat-containing RNA	TERRA

Miscellany

caloric restriction	CR
calorie restriction mimetics	CRMs
combined use of dasatinib and quercetin	DQ
hypothetical ML without the age-related increasing mortality	HML
International Classification of Diseases	ICD
mean duration of life	ML
senescence-associated secretory phenotype	SASP
senescent cell anti-apoptotic pathways	SCAPs
Telomere-Subtelomere-Telomerase system	TST system

Three important definitions:

Telomere - A telomere, from the ancient Greek words τέλος [*télos*, end] and μέρος [*méros*, part], is the ending part of chromosomal DNA molecule and is composed of a repeated short nucleotide sequence (motif), which is very conserved in the course of evolution (e.g., TTAGGG in vertebrates). A telomere is also understood as the association of such a repeated sequence with specialized proteins.

Telomerase - Telomerase is a reverse transcriptase enzyme, i.e., an enzymatic ribonucleoprotein that adds for each cycle a specific nucleotide sequence to telomeric 3' end. The sequence is defined by telomerase RNA and is the same repeated sequence of telomere. Telomerase action compensates for the incomplete duplication of DNA molecule end by the enzyme DNA polymerase and without this action the telomere shortens with each duplication of the DNA molecule.

Subtelomere – Subtelomere, or subtelomeric region, is that part of the chromosomal DNA molecule immediately preceding the telomere. This definition accurately indicates that the subtelomere begins where the telomere ends but does not indicate the other subtelomeric end. In chapter 5 of this book, the subtelomere is defined in functional terms as being composed of two parts:

- Subtelomere R (Regulatory subtelomere) composed of regulatory sequences of first level repressed in proportion to telomere shortening;
- Subtelomere A (Amplifier subtelomere) composed of regulatory sequences of second level regulated by the sequences of subtelomere R. Their action amplifies and multiplies the effects of subtelomere R.

Chapter 1

Introduction

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1.1 - Evolutionary medicine and “evolutionary gerontology and geriatrics”

As medicine is an important part of biology, if “Nothing in biology makes sense, except in the light of evolution” [Dobzhansky 1973] is true, why “Nothing in medicine makes sense, except in the light of evolution” [Varki 2012] should not be true?

“Evolutionary Medicine is the enterprise of using evolutionary biology to address the problems of medicine” [Nesse 2008, p. 417].

Evolutionary medicine is not an alternative medicine (like homeopathy, iridology, ayurvedic medicine, naturopathy, traditional Chinese medicine, energy medicine, etc.), but a more thoroughly scientific medicine, involving the concepts of evolutionism. A medicine that ignored the principles of chemistry, for example, would be partially scientific. Similarly, a medicine that ignores the principles of evolution is partially scientific.

Moreover, just as current medicine encompasses many branches, including that set of cognitions and practical applications that are the subject of gerontology and geriatrics, so too evolutionary medicine must have a similar branch that can be defined as “evolutionary gerontology and geriatrics”. The exposition and discussion of this subject clearly require a brief description and discussion of the main concepts that underlie evolutionary medicine and this will be the topic of *Chapter 3 - Evolutionary medicine*.

However, evolutionary medicine, as it is commonly understood today [Trevathan et al. 1999, 2008a; Stearns and Koella 2008], is still anchored to the traditional concepts of aging conceived as a non-adaptive phenomenon and completely disregards the concept of phenoptosis (adaptive or programmed death of an individual, see below). For a rational and convincing inclusion of gerontology and geriatrics in evolutionary medicine, it is necessary to deepen the concepts of supra-individual selection and phenoptosis and this will be the topic of *Chapter 2 – Evolution and phenoptosis*.

Chapter 3 – Evolutionary medicine, in which the main concepts of evolutionary medicine are outlined, will also be a useful moment to underline some crucial differences between the new and the traditional approach of evolutionary medicine.

1.2 - Definition of aging

There are two different ways to define aging.

The first defines the age-related decline of biological functions as a synonym for aging. Examples of this type of definition are:

Aging is ...

--- “progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age” [Kirkwood and Austad 2000];

--- “a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration” [Rose 1991, p. 20];

--- “any time-dependent change which occurs *after* maturity of size, form, function is reached and which is distinct from daily, seasonal and other biological rhythms” [Rockstein et al. 1977].

The second type of definition makes no reference to alterations of functions and describes the phenomenon simply as an age-related increase in mortality. Examples of this second type of definition are:

Aging is ...

--- “a general title for the group of effects that, in various phyla, lead to a decreasing expectation of life with increasing age” [Comfort 1979, p. 7];

--- “increasing mortality with increasing chronological age in populations in the wild” [Libertini 1988] (Fig. 1.1);

--- “actuarial senescence (declining survivorship with age)” [Holmes and Austad 1995];

--- “increasing mortality with age ... actuarial senescence” [Nussey et al. 2013].

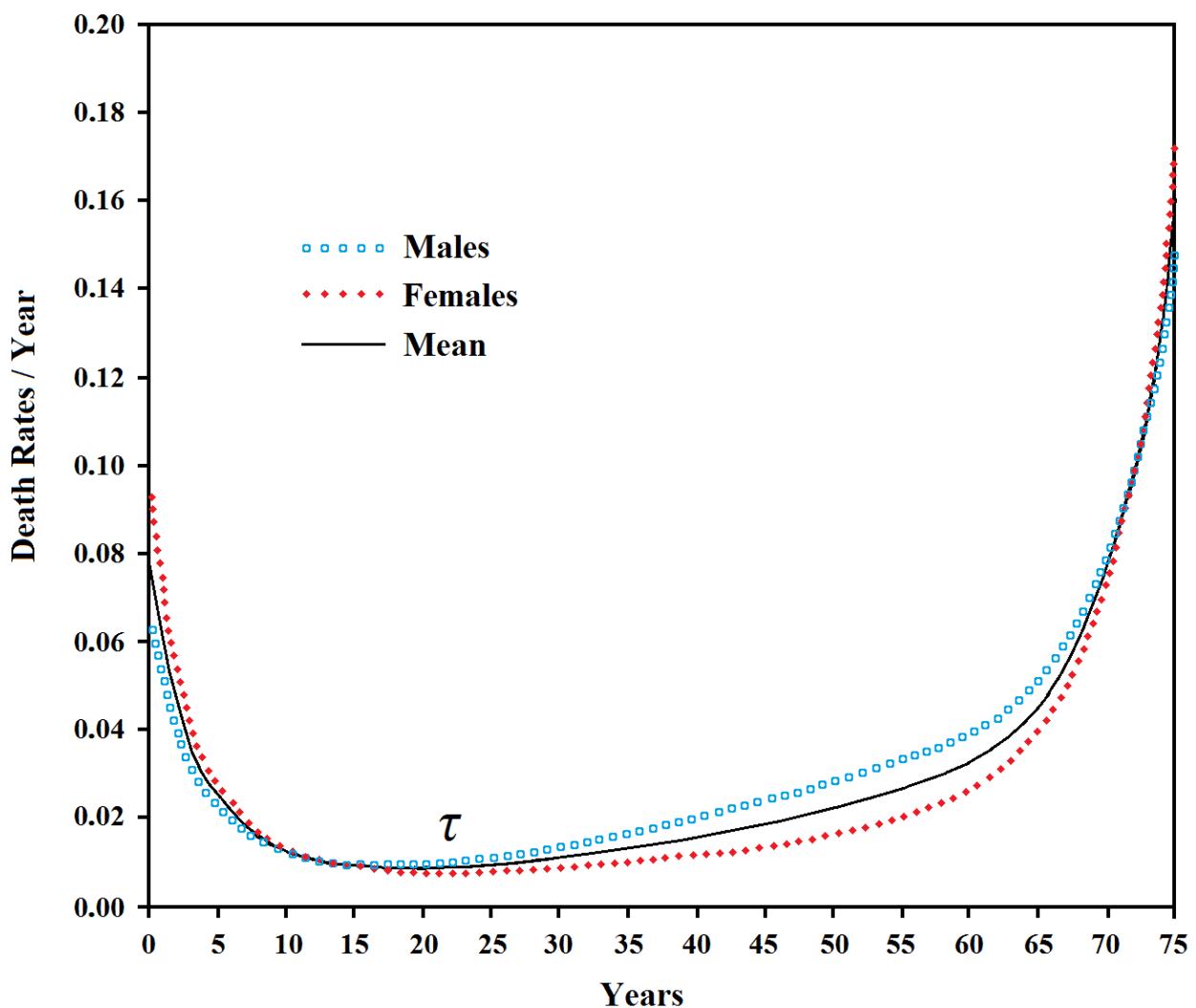


Figure 1.1 – Definition of aging as “increasing mortality with increasing chronological age in populations in the wild” [Libertini 1988]. Death rates of Ache people under natural conditions (forest period) show increasing death rates starting from the period τ ; data from [Hill and Hurtado 1996].

As the decline of biological functions in natural conditions means the decline of Darwinian fitness to survive, i.e., a mortality increase, the first type of definition is equivalent to the second type if the definitions are always restricted to observations in the wild.

However, the second type of definition should be preferred for various reasons.

The increase in the mortality rate can be precisely defined. It is undoubtedly useful to establish the lower arbitrary value of the increase, starting from which the aging is considered to begin. It is also possible to arbitrarily establish a value of the mortality rate (or of the increase of this rate) starting from which an advanced condition of senescence (“state of senility” [Williams 1957]) begins. However, the arbitrary choice of these values does not alter the concept that aging is defined on the basis of a precise parameter, the mortality rate.

On the contrary, how is it possible to define objectively that the modification of a biological parameter is part of aging or not? The problem could be circumvented specifying that the modification of a biological parameter is a manifestation of aging when and to the extent that it reduces fitness, i.e., it increases mortality. Nevertheless, with this specification, the first type of definition becomes synonymous with the second, and at this point, it is better to refer directly to mortality rates regardless of the biological alterations that cause them.

The definition of aging based on biological alterations also entails the dangerous “... confusion of the process of senescence with the state of senility” [Williams 1957]. The state of senility, i.e., the condition of serious alteration of biological functions that characterizes the advanced phases of aging, is not synonymous with aging.

The distinction between aging and the senile state has been well known for some time and is excellently expressed by a Williams’ sentence: “No one would consider a man in his thirties senile, yet, according to athletic records and life tables, senescence is rampant during this decade” [Williams 1957].

The confusion between aging and state of senility has led to deny and diminish the existence of aging in natural conditions and, therefore, to the conclusion that aging cannot be object of natural selection because of its inexistence in nature: “... there is scant evidence that senescence contributes significantly to mortality in the wild. ... As a rule wild animals simply do not live long enough to grow old. Therefore, natural selection has limited opportunity to exert a direct influence over the process of senescence” [Kirkwood and Austad 2000].

1.3 - Aging in natural observation

Until some time ago, doubts were commonly raised about the existence of aging under natural conditions. For example, in 1952, Medawar remarked, “whether animals *can*, or cannot, reveal an innate deterioration with age is almost literally a domestic problem; the fact is that under the exactions of natural life they do not do so. They simply do not live that long” [Medawar 1952]; Rose, in 1991, stated that “... it is doubtful that many individuals would remain for study at the age at which laboratory populations exhibit aging.” [Rose 1991, p. 21]; “Ageing rarely if ever occurs in feral animals because it is unusual for them to live long enough to experience the phenomenon. The same observation can be made for prehistoric humans. Natural selection could not select for a process like ageing when few, if any, animals ever lived long enough to participate in the selection process.” [Hayflick 2000], and just above the belief of two influential authors in 2000, has been reported (“... As a rule wild animals simply do not live long enough to grow old ...” [Kirkwood and Austad 2000]). The idea that only very few individuals survived in the wild long enough to die as a consequence of aging-related mortality was considered as acceptable for a long time [Lack 1954; Berry and Bronson 1992].

However, already in those years, the presence in the wild of age-related increase in mortality has long been known for various species [Libertini 1988; Finch 1990]. In particular, the work of Libertini in 1988 reported data derived from previous field studies that documented aging for seven species of mammals (elephant [Laws 1966], hippopotamus [Laws 1968], waterbuck [Spinage 1970], Dall mountain sheep [Deevey 1947], zebra, warthog, impala and buffalo [Spinage 1972]). In 1998, an authoritative paper [Ricklefs 1998] further documented the age-related mortality increase for populations under natural conditions.

An example of a life table with age-related increasing mortality, based on data from natural observation [Ricklefs 1998], is illustrated in Fig. 1.2.

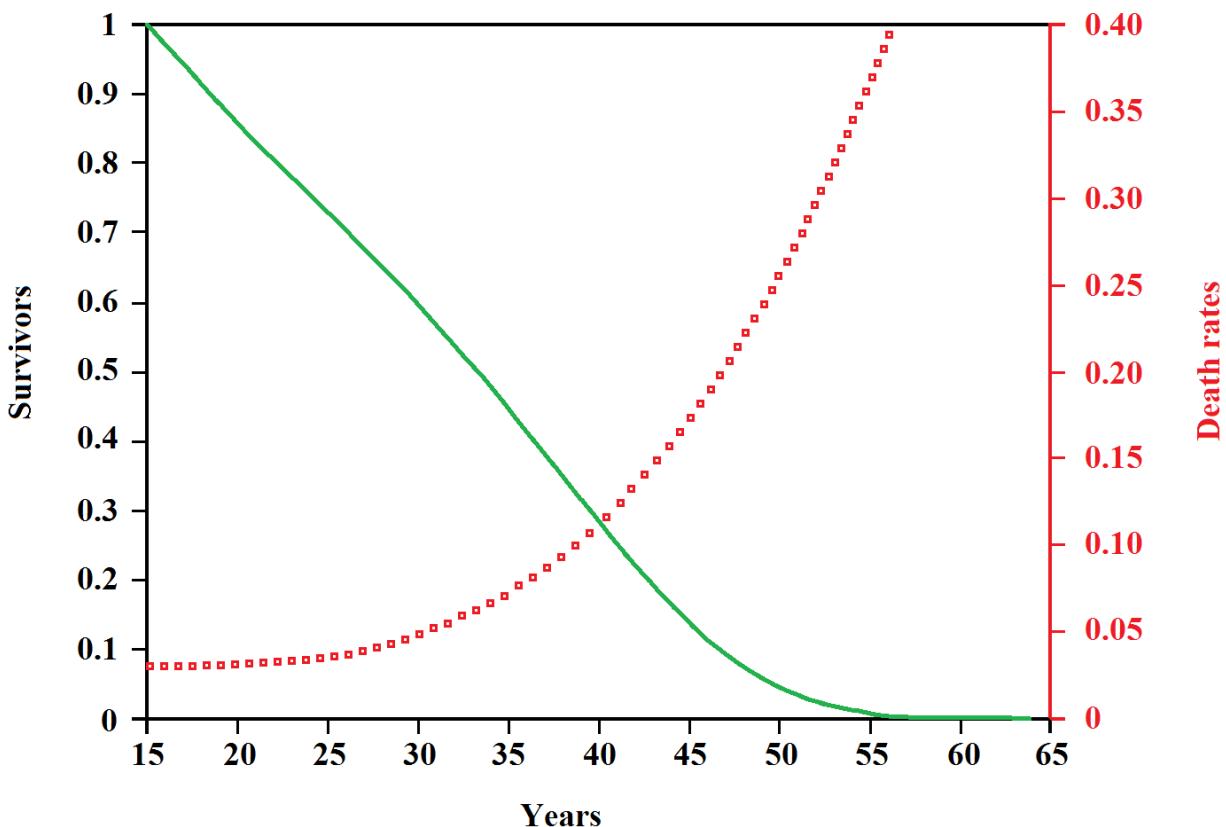


Figure 1.2 - Life table and mortality of *Hippopotamus amphibius*, sex combined, in the wild (Data from [Ricklefs 1998]). The survivors and the high mortality in the first years are not reported.

A subsequent authoritative review [Nussey et al. 2013], widely confirmed the existence of an age-related mortality increase for many species studied in the wild. In particular, the study stated that: “The recent emergence of long-term field studies presents irrefutable evidence that senescence is commonly detected in nature. We found such evidence in 175 different animal species from 340 separate studies.” [Nussey et al. 2013]. It is interesting to note that one of the authors of the study, Steven Austad, is the same one who, together with Kirkwood, in 2000 denied the existence of senescence under natural conditions [Kirkwood and Austad 2000].

A closely related topic is the extent to which aging contributes to changing the mean duration of life span (“ML”) in natural conditions. Kirkwood and Austad [Kirkwood and Austad 2000], as reported before, maintained that aging, being practically absent under natural conditions, had little or no influence in reducing the chances of survival, and therefore it was not a phenomenon modifiable by natural selection.

This position was already untenable in 2000 as it was contradicted by data deriving from the observation of animal communities in the wild. In fact, in a 1988 work already mentioned [Libertini 1988] and based on known pre-existing data, it was shown that the ML would have doubled approximately if there had not been an age-related increase in mortality. Furthermore, excluding individuals who died during the first period of life, which is characterized by high mortality, the residual ML of the considered subpopulation ($ML\tau$) tripled in the hypothetical absence of an increase in age-related mortality (see Table 1.1).

Table 1.1 – Influence of aging on ML (Table 1 in [Libertini 1988], modified; all times are in years).

Legend:

τ = age when the death rate is the lowest;

λ_{\min} = mortality at the age τ ;

ML = ML observed in the wild;

HML = hypothetical ML without the age-related increasing mortality;

$ML\tau - \tau$ = [ML observed in the wild for the individuals survived at time τ] – [τ];

$HML\tau - \tau$ = [hypothetical ML of the individuals survived at time τ without the age-related increasing mortality] – [τ].

Species [source of data]	τ	λ_{\min}	ML (A)	HML (B)	Ratio B/A	ML $\tau - \tau$ (C)	HML $\tau - \tau$ (D)	Ratio (D/C)
Zebra [Spinage 1972]	6	4.63	8.48	17.23	2.03	6.73	21.55	3.20
Hippopotamus [Laws 1968]	14	1.03	15.40	43.33	2.81	21.69	96.68	4.45
Elephant [Laws 1966]	16	1.95	17.27	28.85	1.67	21.08	51.95	2.42
Waterbuck [Spinage 1970]	3	5.55	3.71	9.56	2.57	4.47	18.00	4.02
Warthog [Spinage 1972]	8	5.90	4.79	7.43	1.55	5.92	16.93	2.85
Impala [Spinage 1972]	3	5.44	6.37	16.87	2.64	4.76	18.35	3.85
Buffalo [Spinage 1972]	5	4.23	5.50	12.16	2.21	6.80	23.61	3.46
Dall mountain sheep [Deevey 1947]	4	3.54	7.15	23.00	3.21	5.52	28.17	5.09
				Mean =	2.34		Mean =	3.67

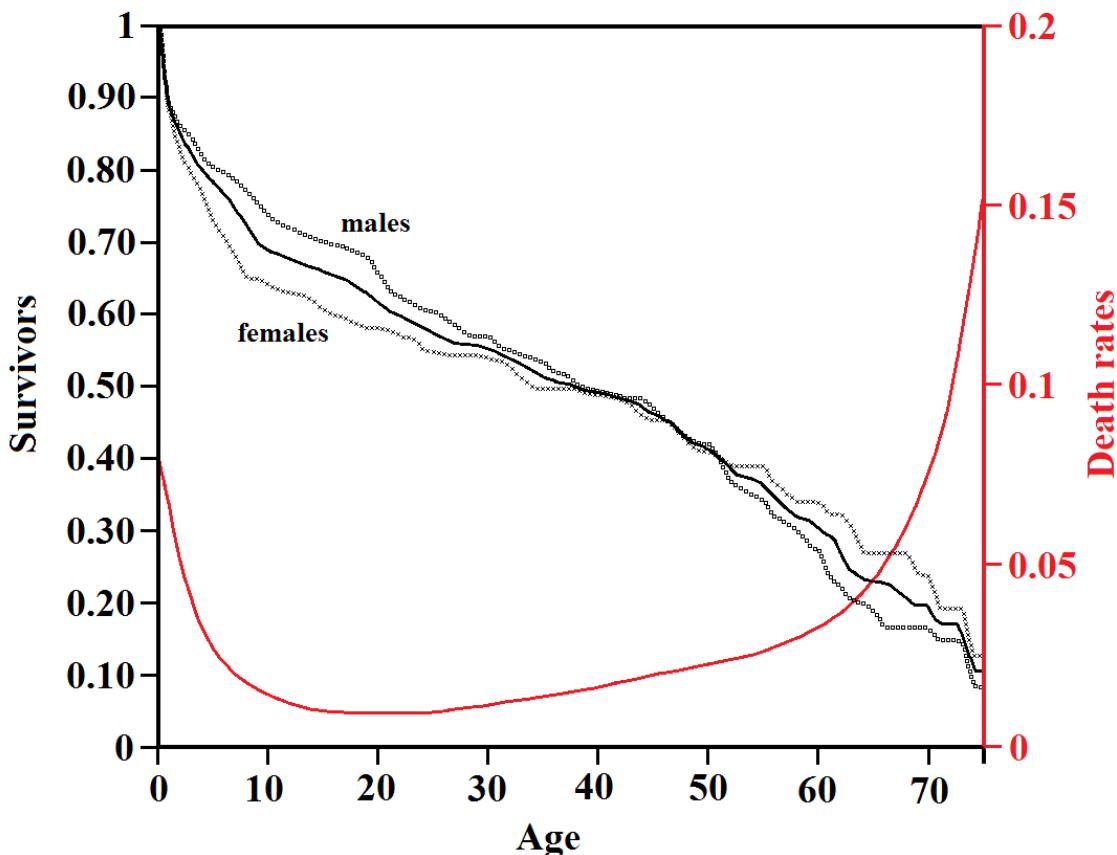


Figure 1.3 – Survivors and death rates of Ache population (in the forest period) (data from [Hill and Hurtado 1996]).

A subsequent work of 1998 [Ricklefs 1998] also showed for a higher number of species that, under natural conditions, the proportion of deaths due to aging (P_s) was considerable and such as to reduce the duration of life significantly.

After the work of Kirkwood and Austad [Kirkwood and Austad 2000], further data have denied their firm belief. As before said, in 2013, an important work [Nussey et al. 2013] reviewed a significant number of papers demonstrating that for many species, an age-related increase in mortality exists in natural conditions and undoubtedly influences the mean duration of life.

In the same year, another work [Libertini 2013] discussed data from a human population (Ache people of Paraguay) under natural conditions in a critical observational study on the field [Hill and Hurtado 1996]. This study documented an age-related mortality increase that started from the third decade of life (the same period of life highlighted by Williams [Williams 1957] for modern populations). Despite the primitive conditions of life and the high mortality due to violent causes or to other causes that would be lethal at any age, about 31%, 24%, 21% and 11% of the individuals survived at the ages of 60, 65, 70 and 75 years, respectively [Hill and Hurtado 1996] (Fig. 1.3).

Moreover, it was calculated the ML in the hypothetical case of no age-related mortality increase, both considering the whole population (Fig. 1.4) and considering only the survivors at the age of 20 years when the mortality was at its lowest value (Fig. 1.5).

In the first case, the ML under natural conditions for the whole population was equal to 38.8 years, while hypothetically excluding any age-related mortality increase the ML reached 87.75 years with a ratio between the two values equal to 2.26.

In the second case, i.e., considering only the individuals surviving at the age of 20 years (when the mortality had its lowest value, about 0.858%/year), the ML was $20 + 38.1 = 58.1$ years, while for the hypothetical curve where age-related increasing mortality was excluded, the ML was $20 + 116.55 = 136.55$ years, with a ratio between the years survived after the age of 20 years equal to $116.55/38.1 = 3.059$. These data were equivalent to those obtained for the other species reported in Table 1.1.

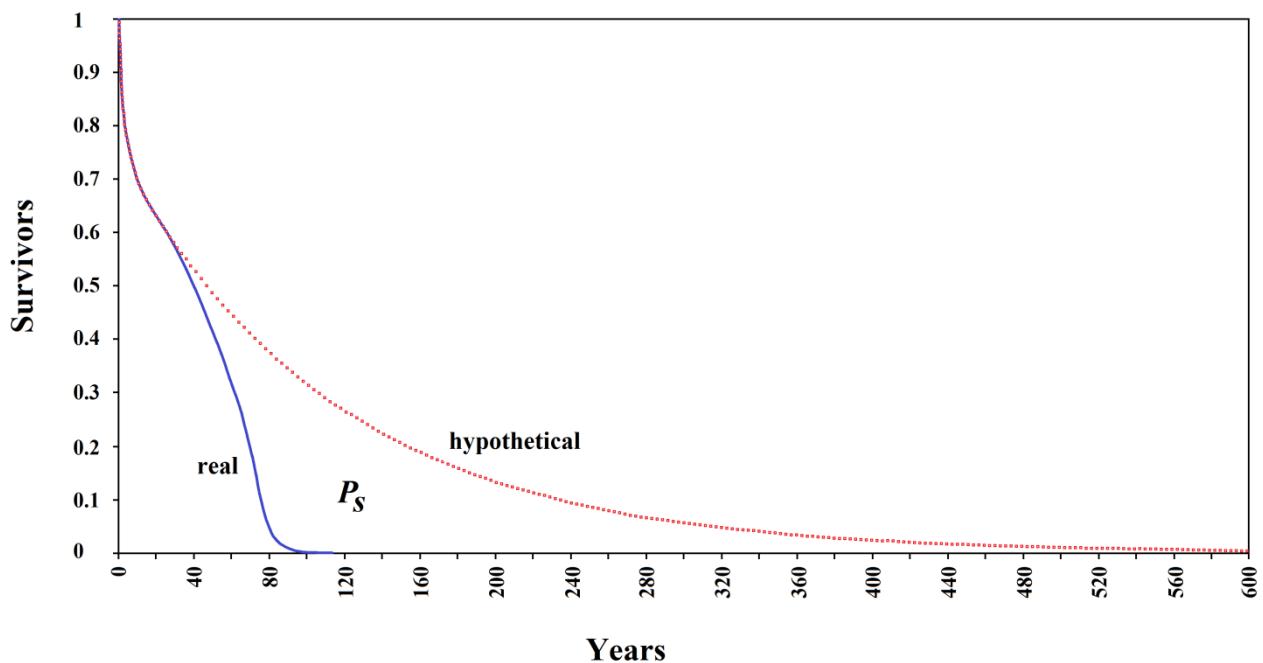


Figure 1.4 – The continuous line shows the real life table of Ache people in the wild (forest period; data from [Hill and Hurtado 1996]), while the dashed line indicates the hypothetical life table without age-related increasing mortality. P_s area indicates the proportion of deaths due to aging (definition of P_s from [Ricklefs 1998]). Abscissas extend as far as 600 years, as at the age of 580 about 0.5% of the population would survive if the mortality is constant with a rate of 0.9%/year (about the estimated minimum mortality in natural conditions).

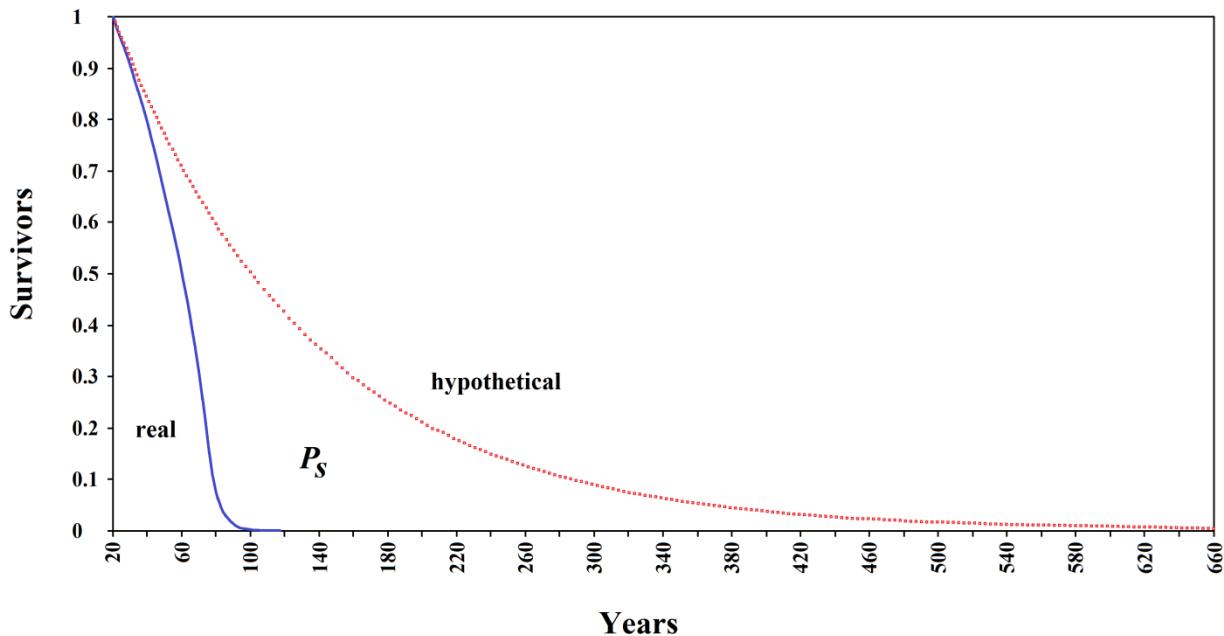


Figure 1.5 - The same as in the previous figure, but only individuals surviving at the age of 20 years are considered. Abscissas extend as far as 660 years since - with a constant mortality rate of 0.9%/year - at the age of 634 years about 0.5% of the population would survive.

These studies confirmed the concept that the definition of aging as increasing mortality with increasing chronological age in populations in the wild, or other equivalent definitions, describes a phenomenon that exists in natural conditions and significantly reduces lifespan, which is a strong and essential starting point.

1.4 - A short history of aging theories

A brief history of the concepts and theories about aging and its interpretation is now useful and necessary.

As in any historical description, the arbitrary division into periods implies in itself a subjective interpretation. Moreover, whatever are the adopted criteria, there will always be many events that temporally fall in a period but reflect the characteristics of other periods. The following parts of this section try to divide the history of aging theories into three periods.

1.4.1 – The conception of aging up to 19th century

As Comfort says: "... senescence enters human experience through the fact that man exhibits it himself. This close involvement with human fears and aspirations may account for the very extensive metaphysical literature on ageing. It certainly accounts for the profound concern with which humanity has tended to regard the subject. To a great extent human history and psychology must always have been determined and moulded by the awareness that the life-span of any individual is determinate, and that the expectation of life tends to decrease with increasing age. The Oriental could say *O King, live for ever!* in the knowledge that every personal tyranny has its term. Every child since the emergence of language has probably asked *Why did that man die?* and has been told *He died because he was old.*" [Comfort 1979, pp. 1-2]

Always, up to Darwin and beyond, the observation that every material object with time deteriorates and gradually consumes, has rooted in everyone, even in the greatest philosophers, the idea that this was true also for every living being, including man. As explained to the child, we do not age for some specific reason, but only because time passed and we became old, i.e., worn and altered, like

everything else. There was no need for other explanations for such a trivially obvious category of events.

In the Greek classic culture, immortality and eternal youth were prerogatives of the deities that mortals could not have. A mortal that presumed to compete with the gods, searching for being like to them, for example, aspiring to immortality, became guilty of *úþρις*, namely of impious pride and arrogance toward the deity.

There was also full awareness of the distinction between immortality and eternal youth. It is known the myth of Eos (Aurora), who asked Zeus (Jupiter) for the immortality of the beloved Tithonus. Zeus consented to Eos' request, but she had forgotten to ask also for the eternal youth for the beloved. So Tithonus did not die but became ever older and decrepit until Zeus moved to pity and consented to Eos' new request to end this torment turning Tithonus into an animal [Comfort 1979]. However, a fact considered inevitable found its fantastic remedies in myths and fantasies. For example, medieval alchemists strenuously sought to obtain the philosopher's stone that would have given both the ability to transform lead into gold and to obtain an elixir of life that would have allowed an eternal youth and immortality [Comfort 1979].

Then there was the myth of the Fountain of Youth, born with Herodotus: "The Ichthyophagi then in their turn questioned the king [of Ethiopians] concerning the term of life, and diet of his people, and were told that most of them lived to be a hundred and twenty years old, while some even went beyond that age - they ate boiled flesh, and had for their drink nothing but milk. When the Ichthyophagi showed wonder at the number of the years, he led them to a fountain, wherein when they had washed, they found their flesh all glossy and sleek, as if they had bathed in oil - and a scent came from the spring like that of violets. The water was so weak, they said, that nothing would float in it, neither wood, nor any lighter substance, but all went to the bottom. If the account of this fountain be true, it would be their constant use of the water from it which makes them so long-lived." [Herodotus, *The histories*, book III, 23].



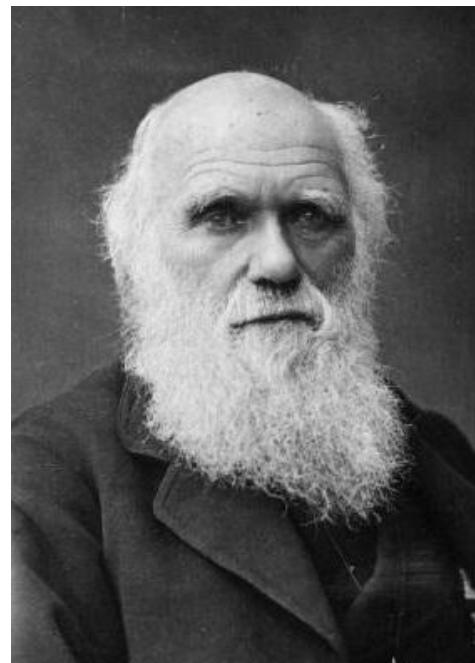
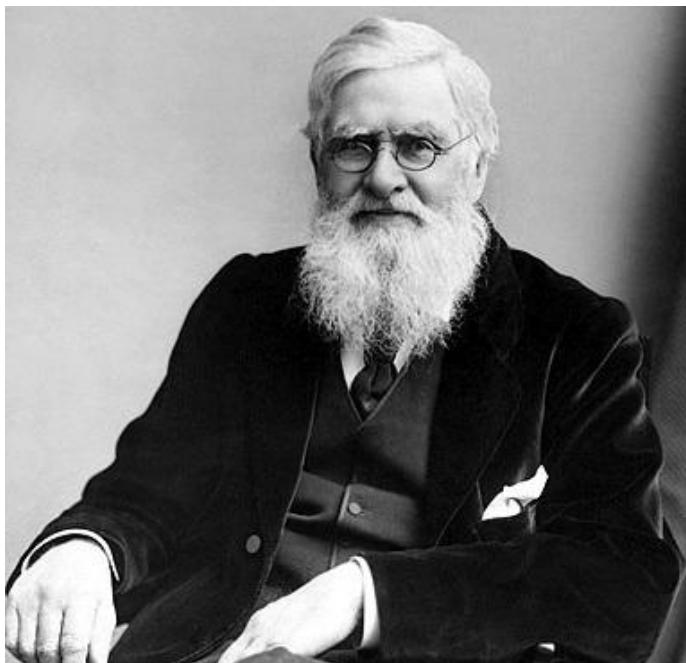
Figure 1.6 - Lucas Cranach the Elder, *The Fountain of Youth*, 1546.

This myth persisted in the Middle Ages (Fig. 1.6) and was reinvigorated with the discovery of the Americas. Gonzalo Fernández de Oviedo y Valdés wrote in 1535 that Ponce de Leon was looking for the waters of Bimini (in the modern Bahamas) to regain youthfulness [de Oviedo, 16th century, book 16, chapter XII]. In 1575, Hernando d'Escalante Fontaneda, who had lived with the Native Americans of Florida for 17 years, in his memoirs located the mythical waters in Florida and maintained that Ponce de León was supposed to have looked for them there [Fontaneda 1575].

1.4.2 - Aging theories in the 19th century and the first half of the 20th century

In the nineteenth century, before and after the publication of Charles Darwin's revolutionary book [Darwin 1859], there was a flourishing of studies in every field of biology. They certainly could not miss the subject of the mechanisms underlying the progressive decay of individuals over time. Evolution by natural selection changed the conception of the whole biology and, therefore, potentially also the concepts underlying aging, but this was understood long afterward. In fact, the pivotal concept of evolution in its first Darwinian formulation, i.e., natural selection based on the "survival of the fittest" [Darwin 1869], was in clear contrast with the possibility that selection could favor something that certainly damaged the individual in a total and unequivocal way.

As a matter of fact, the expression "survival of the fittest" was coined by Herbert Spencer [Spencer 1864] and adopted later by Darwin in the fifth edition of his book ("Natural Selection or the Survival of the Fittest" [Darwin 1869]). However, Darwin did not rule out the possibility that natural selection could foster characters that are harmful to the individual. For example, he says: "A tribe including many members who ... were always ready to aid one another, and to sacrifice themselves for the common good, would be victorious over most other tribes; and this would be natural selection." [Darwin 1871, p. 500]



Figures 1.7 and 1.8 - Alfred Russel Wallace (1823-1913), on the left, conceived the theory of evolution through natural selection independently from Charles Robert Darwin (1809-1882), on the right. His proposal and that of Darwin were jointly published in 1858.

Yet, the common interpretation of Darwinian ideas was that natural selection always favored traits that were beneficial for the individual and therefore aging did not seem conceivable as a phenomenon favored by natural selection.

There were only two exceptions in this unanimous chorus. Alfred Russel Wallace (Fig. 1.7), who had proposed with Charles Robert Darwin (Fig. 1.8) the evolution by natural selection, was the first

to guess, with extraordinary intuition, that aging could be an adaptive phenomenon in one of his letters, written in an unspecified year around 1865-1870, as reported by August Weismann: "... for it is evident that when one or more individuals have provided a sufficient number of successors, they themselves, as consumers of nourishment in a constantly increasing degree, are an injury to those successors. Natural selection therefore weeds them out, and in many cases favors such races as die almost immediately after they have successors." [Wallace 1865-1870 in Weismann 1889, vol. I]

This principle was later developed by the same Weismann (Fig. 1.9), who hypothesized that the anticipated death of old individuals was beneficial because this gave more space to new generations, and this favored the evolution of the species [Weismann 1889, vol. I, 1891]: "... To put it briefly, I consider that duration of life is really dependent upon adaptation to external conditions, that its length, whether longer or shorter, is governed by the needs of the species, and that it is determined by precisely the same mechanical process of regulation as that by which the structure and functions of an organism are adapted to its environment" [Weismann 1891, pp. 6-10]; "Worn out individuals are not only valueless to the species, but they are even harmful, for they take the place of those which are sound. Hence by the operation of natural selection, the life of our hypothetically immortal individual would be shortened by the amount which was useless to the species" [Weismann 1891, pp. 24-25].

"... the reason suggested by Weismann for the evolution of ageing was an adaptive one, namely that ageing is beneficial in ridding a species of old and decrepit individuals which would otherwise compete for resources with younger ones. Thus, by natural selection the somatic cells of the organism would have come to lose their capacity for unlimited survival, and ageing of the organism as a whole would have appeared." [Kirkwood and Cremer 1982]

So, after Wallace, Weismann proposed an adaptive meaning of aging again and was also the first to hypothesize that the mechanism underlying aging was the slowing or blocking of cell and tissue renewal [Kirkwood and Cremer 1982]: "... death takes place because a worn-out tissue cannot forever renew itself, and because a capacity for increase by means of cell-division is not everlasting, but finite" [Weismann 1891, p. 21]; "... the organism did not finally cease to renew the worn-out cell material because the nature of the cells did not permit them to multiply indefinitely, but because the power of multiplying indefinitely was lost when it ceased to be of use" [Weismann 1891, p. 25]. However, Weismann did not explain and justify the proposal of an adaptive meaning of aging in more detail, was attacked as an anti-Darwinist even though Darwin had hypothesized the sacrifice of individuals "for the common good" [Darwin 1871, p. 500], and after a few years repudiated this idea [Weismann 1892; Kirkwood and Cremer 1982]. Moreover, the hypothesis that limits in cell reproductive capacities were the main mechanism of senescence appeared falsified, a few years later, by the erroneous experiments of Carrel that seemed to demonstrate an unlimited capacity of cellular reproduction [Carrel 1912, 1913; Carrel and Ebeling 1921a]. Only when Hayflick's experiments proved false those of Carrel [Hayflick and Moorhead 1961; Hayflick 1965], this forgotten hypothesis became again acceptable.

Apart from these exceptions, for long time research on the causes of aging ignored the mechanisms of evolution and tried to identify the causes of aging in a series of chemical or physical factors.

In this period, about aging, while Darwinian ideas were disregarded, there was a vast array of putative causes of aging, of which many could be defined as "Damage Accumulation hypotheses".

They proposed that aging is due to the cumulative effect of damages of various kinds, e.g.:

- cellular "wear and tear" [Weismann 1882; Pearl 1928; Warthin 1929];
- mechanochemical deterioration of cell colloids [Bauer 1924; Bergauer 1924; Růžická 1924, 1929; Lepeschkin 1931; Szabó 1931; Dhar 1932; Marinesco 1934; Kopaczewski 1938; Georgiana 1949];
- inherent changes in specified tissues:
 - nervous [Mühlmann 1900, 1924, 1927; Ribbert 1908; Vogt and Vogt 1946; Bab 1948];
 - endocrine [Lorand 1904; Gley 1922; Dunn 1946; Findley 1949; Parhon 1955];

- vascular [Demange 1886];
- connective [Bogomolets 1947];
- toxic products of intestinal bacteria [Metchnikoff 1904, 1907; Lorand 1929; Metalnikov 1937] (Fig. 1.10);
- accumulation of “metaplasma” or of metabolites [Kassowitz 1899; Jickeli 1902; Montgomery 1906; Mühlmann 1910; Molisch 1938; Lansing 1942; Heilbrunn 1943];
- action of gravity [Darányi 1930];
- accumulation of heavy water [Hakh and Westling 1934] (a hypothesis proposed again in 1973 [Griffiths 1973]);
- the effect of an Aristotelian “entelechy” [Driesch 1941; Bürger 1954];
- metabolic theories introducing the concept of a fixed-quantity reaction or of a rate/quantity relationship in determining longevity [Loeb 1908; Rubner 1908; Robertson 1923; Pearl 1928];
- attainment of a critical volume-surface relationship [Mühlmann 1910];
- depletive theories relating senescence to reproduction [Orton 1929].

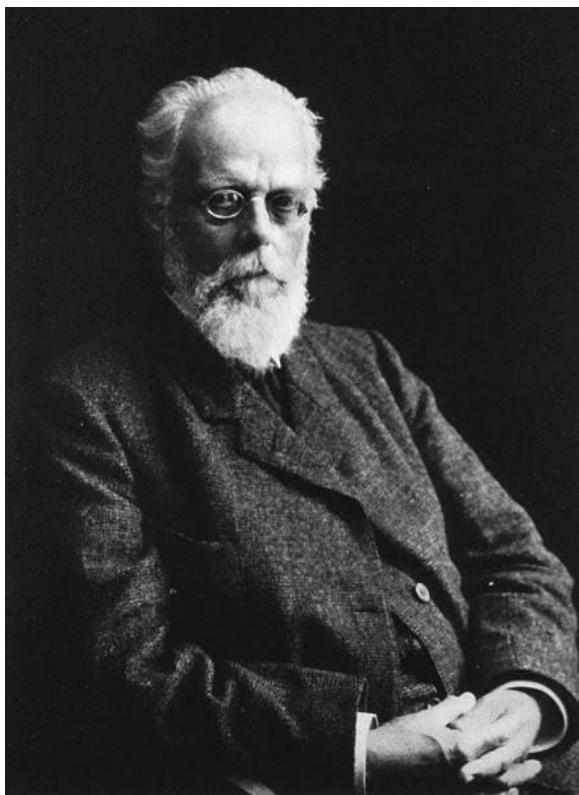


Figure 1.9 - Friedrich Leopold August Weismann (1834-1914) is considered the second most notable evolutionary theorist of the 19th century, after Charles Darwin, and one of the founders of Neo-Darwinism.

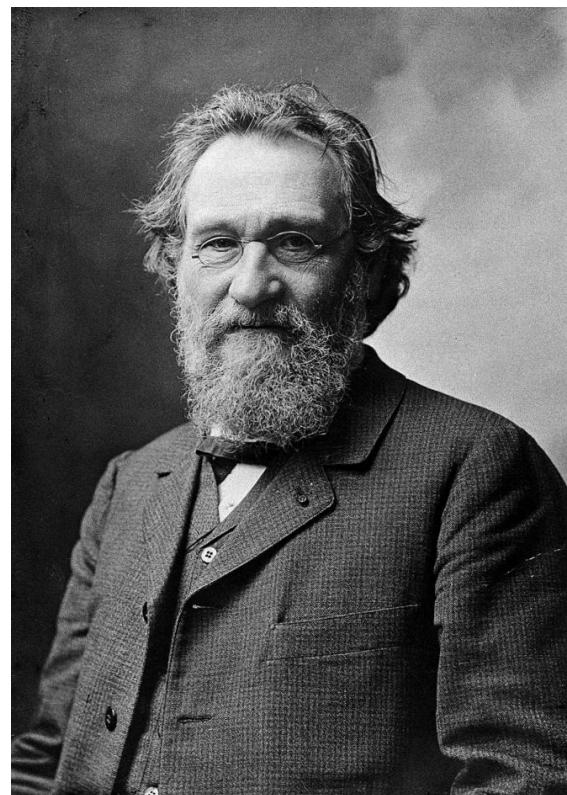


Figure 1.10 - Élie Metchnikoff (1845-1916), the winner of the 1908 Nobel Prize in Physiology or Medicine with Paul Ehrlich, for his research on phagocytosis and immunity, proposed that aging is caused by toxic bacteria in the gut and that lactic acid could prolong life.

The nineteenth century was also the epoch in which the concept of entropy (disorder of a system) and the general theorem that, in a closed system, the entropy could only increase were proposed. Consequently, by interpreting aging as a condition of greater organism disorder, the phenomenon was explained as the consequence of age-related necessarily growing disorder of the organism. This hypothesis disregarded the fact that any organism is not a closed system and can live only because it receives energy from the outside (plants from the light of the sun through photosynthesis, animals from plants and other animals, etc.). Therefore, an inevitable increase in entropy is not expected in living systems, and neither is a valid justification for aging. Yet, even today, someone tries to

justify aging as being due to the inevitable increase in entropy. Hayflick (!) some years ago stated for sure: “There is a huge body of knowledge supporting the belief that age changes are characterized by increasing entropy, which results in the random loss of molecular fidelity, and accumulates to slowly overwhelm maintenance systems.” [Hayflick 2007a]



Figure 1.11 - Charles Sedgwick Minot (1852-1914).



Figure 1.12 - George Parker Bidder III (1863-1953).

A different group of theories related aging to:

- continuity of senescence with morphogenesis [Baer 1864; Roux 1881; Cholodkowsky 1882; Delage 1903; Warthin 1929];
- cessation of somatic growth [Minot 1908; Carrel and Ebeling 1921b; Brody 1924; Bidder 1932; Lansing 1948, 1951] (Figs. 1.11 and 1.12).

An example of how in this period the aging problem was addressed in “scientific terms” is as follows: “The Universe, by its very nature, demands mortality for the individual if the life of the species is to attain immortality through the ability to cope with the changing environment of successive ages. ... It is evident that *involution* is a biologic entity equally important with *evolution* in the broad scheme of the immortal process of life. Its processes are as *physiologic* as those of growth. It is therefore inherent in the cell itself, an intrinsic, inherited quality of the germ plasm and no slur or stigma of *pathologic* should be cast upon this process. What its exact chemicophysical mechanism is will be known only when we know the nature of the *energy-charge* and the *energy-release* of the cell. We may say, therefore, that age, the major involution, is due primarily to the gradually weakening energy-charge set in action by the moment of fertilization, and is dependent upon the potential fulfilment of function by the organism. The immortality of the germ plasm rests upon the renewal of this energy charge from generation to generation.” [Warthin 1929] (reported in [Comfort 1979, p. 8]).

1.4.3 - Aging theories from the second half of the 20th century to today

In the second half of the twentieth century, the new idea was that the study of aging causes could not disregard the mechanisms of natural selection. Thus, some “evolutionary” theories of aging were proposed:

- *Mutation accumulation hypothesis*. As at older ages few individuals survive, natural selection becomes increasingly weak. So harmful genes that act late in life are scarcely removed by

natural selection and aging results from their combined effects [Medawar 1952; Hamilton 1966; Edney and Gill 1968; Mueller 1987; Partridge and Barton 1993] (Figs. 1.13 and 1.14).

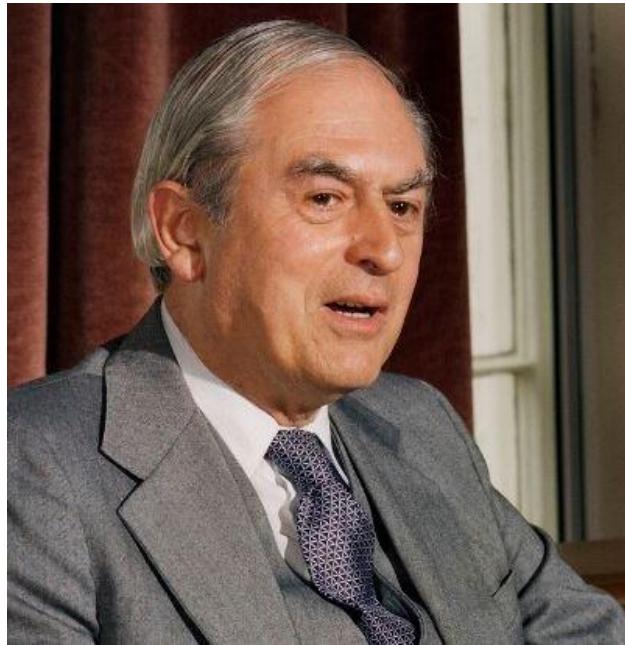


Figure 1.13 - Peter Brian Medawar (1915-1987).

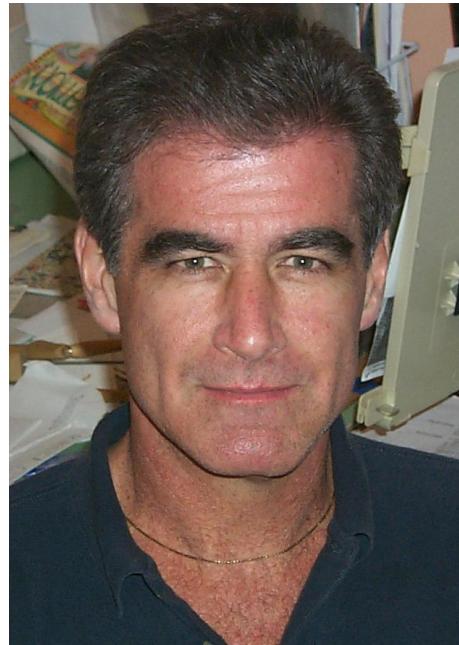


Figure 1.14 - Laurence D. Mueller.



Figure 1.15 - George Christopher Williams (1926-2010).



Figure 1.16 - Michael R. Rose.

- *Antagonistic pleiotropy hypothesis.* It is hypothesized the existence of certain genes that are both advantageous during young or adult stage and disadvantageous at older ages. Therefore, they are only partially eliminated by natural selection and their effects at older ages are the cause of aging [Williams 1957; Rose 1991] (Figs. 1.15 and 1.16).
- *Disposable soma hypothesis.* The organism has limited energetic and metabolic resources. Therefore, the body, in the allocation of these limited resources, must divide them between the necessities of a greater reproductive capacity and those of a better efficiency of maintenance

systems. The insufficiency of these systems jeopardizes the functions of the organism at older ages, and so the body (i.e., the soma) is sacrificed to meet the needs of reproduction. [Kirkwood 1977; Kirkwood and Holliday 1979] (Fig. 1.17).

- *Quasi-programmed senescence hypothesis* [Blagosklonny 2006] (Fig. 1.18): “nature blindly selects for short-term benefits of robust developmental growth ... aging is a wasteful and aimless continuation of developmental growth” [Blagosklonny 2013]. This hypothesis appears to continue some aspects of another previous theory that suggests a neuroendocrine mechanism of ageing, in particular a general hormonal imbalance due to a gradual alteration of the hypothalamic functions [Dilman 1971; Dilman and Anisimov 1979]. In analogy to the *Disposable soma hypothesis*, it is likely that this alteration could not be eliminated from natural selection due to conflicting metabolic needs.



Figure 1.17 - Thomas Burton L. Kirkwood (1951).



Figure 1.18 - Mikhail V. Blagosklonny.

These “evolutionary” theories of aging are united by the assumption that aging, as it is certainly harmful in individual terms, cannot be a result of natural selection like other characteristics of living beings. So, natural selection can only act against the factors that cause aging but for various reasons its action is weakened and curbed and therefore we get older.

In the same period, however, other theories were proposed that explained aging as the result of natural selection at the supra-individual level.

- In 1961, Aldo Carl Leopold, a botanist, proposed that aging increased the speed of evolutionary adaptability of a species: “... in plants senescence is a catalyst for evolutionary adaptability” [Leopold 1961]. Leopold followed the hint of Weismann, again suggesting that aging favors evolution as it accelerates generation turnover. Besides, he proposed that aging was determined by specific mechanisms: “We can safely assume that there are some internal biological mechanisms which bring about decline in viability and increase in vulnerability in such populations.” [Leopold 1961]. This is a clear definition of aging as a phenomenon genetically determined and programmed.
- In 1988 (anticipated in 1983 in a non-peer reviewed book [Libertini 1983]), a theory was proposed that explained aging as an adaptive phenomenon. According to this hypothesis, aging was favored by natural supra-individual selection, in terms of kin selection, in particular ecological conditions (spatially structured populations and K-selection) [Libertini 1988] (Fig. 1.19). This

hypothesis was later reaffirmed and, among other things, for the first time, an inverse relationship between the proportion of senescent deaths and the extrinsic mortality was predicted [Libertini 2006, 2008, 2009a, 2013].

- In 2004 and afterward, other authors proposed theories that pointed out an evolutionary advantage for aging in spatially structured populations [Travis 2004; Martins 2011; Yang 2013; Mitteldorf and Martins 2014] (Figs. 1.20, 1.21 and 1.22).
- Following Weismann's insight, Goldsmith proposed that aging is favored by natural selection because it increases the speed of evolution, or evolvability [Goldsmith 2004, 2008] (Fig. 1.23).
- Consistently with the idea of aging as a programmed phenomenon favored by natural selection, the damage induced by mitochondrial reactive oxygen species (mtROS) was proposed as a pivotal mechanism [Skulachev 1999a, 2001; Skulachev and Longo 2005]. The same Skulachev (Fig. 1.24) in 1997 defined aging as a form of "phenoptosis", a neologism indicating the cases of programmed death determined by the same organism [Skulachev 1997, 1999b], and a few years later defined more precisely aging as "slow phenoptosis" [Skulachev 2002a].
- In 2009, a theory proposed that aging was an adaptation to limit the spread of diseases by a mechanism that was analogous to the Red Queen hypothesis on the adaptive meaning of sex [Mitteldorf and Pepper 2009].



Figure 1.19 - Giacinto Libertini.



Figure 1.20 - Justin M. Travis.



Figure 1.21 – André C. Martins.



Figure 1.22 - Josh Mitteldorf.



Figure 1.23 - Theodore C. Goldsmith.

In 2008, it was pointed out that there were some common logical predictions for all programmed aging theories. In fact, they predicted (i) the existence of non-aging species, i.e., without any age-related increase of mortality; (ii) in the comparison among different species, an inverse relation between the proportion of senescent deaths and extrinsic mortality; and (iii) the existence of specific, genetically determined and modulated, mechanisms that caused aging. It was also pointed out that these predictions were in clear contrast with those of non-programmed aging theories [Libertini 2008].

In this same period theories classifiable in the group of Damage Accumulation hypotheses and that disregard the mechanisms of natural selection continued to be proposed. According to these theories, in a summary list, aging is due to:

- accumulation of chemical damage due to DNA transcription errors [Weinert and Timiras 2003];
- deleterious effects of oxidation [Molnár 1972];
- oxidative effects of free radicals on the whole body [Harman 1956; Croteau and Bohr 1997; Beckman and Ames 1998; Oliveira et al. 2010] (Fig. 1.25);
- oxidative effects of free radicals on the mitochondria [Harman 1972; Miquel et al. 1980; Trifunovic et al. 2004; Balaban et al. 2005; Sanz and Stefanatos 2008];
- oxidative effects of free radicals on the DNA [Bohr and Anson 1995; Weinert and Timiras 2003];
- inflammatory phenomena (“inflamm-aging”) and immunological alterations related to age [Franceschi et al. 2000; Fülöp et al. 2014; Fülöp 2017; Franceschi et al. 2018] (Figs. 1.26 and 1.27), which characterize aging. They were explained not as consequences but as causes of aging.

1.4.4 - Classification of aging theories

The theories that try to explain the causes of aging [Comfort 1979; Medvedev 1990; Weinert and Timiras 2003; Libertini 2015a] may be divided in: (A) non-evolutionary; and (B) evolutionary theories, according to the non-consideration or consideration of natural selection as a possible factor that could influence or determine the aging.

A second division is between: (C) non-programmed or non-adaptive aging theories; and (D) programmed or adaptive aging theories.

For the theories of the first group (C), aging is due to damaging or degenerative phenomena that natural selection cannot oppose with sufficient strength. So aging is considered as a *failure* of natural selection.



Figure 1.24 - Vladimir Skulachev.



Figure 1.25 - Denham Harman (1916-2014).



Figure 1.26 – Claudio Franceschi.



Figure 1.27 - Tamas Fülöp.

On the contrary, for the theories of the second group (D), aging, although harmful to the individual, is favored by supra-individual natural selection. Therefore, aging, since it is forged by natural selection, must be determined by mechanisms that are genetically determined and modulated and must be considered as a *success* of evolution.

The theories of group C (non-adaptive theories) include the whole group A (non-evolutionary theories) and part of group B (evolutionary theories), while the theories of the group D (adaptive theories) are all within the group B (evolutionary theories) (see a schematization in Fig. 1.28).

While the distinction between theories of the groups A and B (non-evolutionary and evolutionary theories) is not always clear-cut, the distinction between the group C and D is reliable and complete, as they have opposite premises and outcomes and there is no possible form of compromise. Therefore these two opposite types of interpretations of the aging phenomenon deserve the definition of opposite paradigms [Libertini 2009a], in the meaning of the term defined by Kuhn [Kuhn 1962].

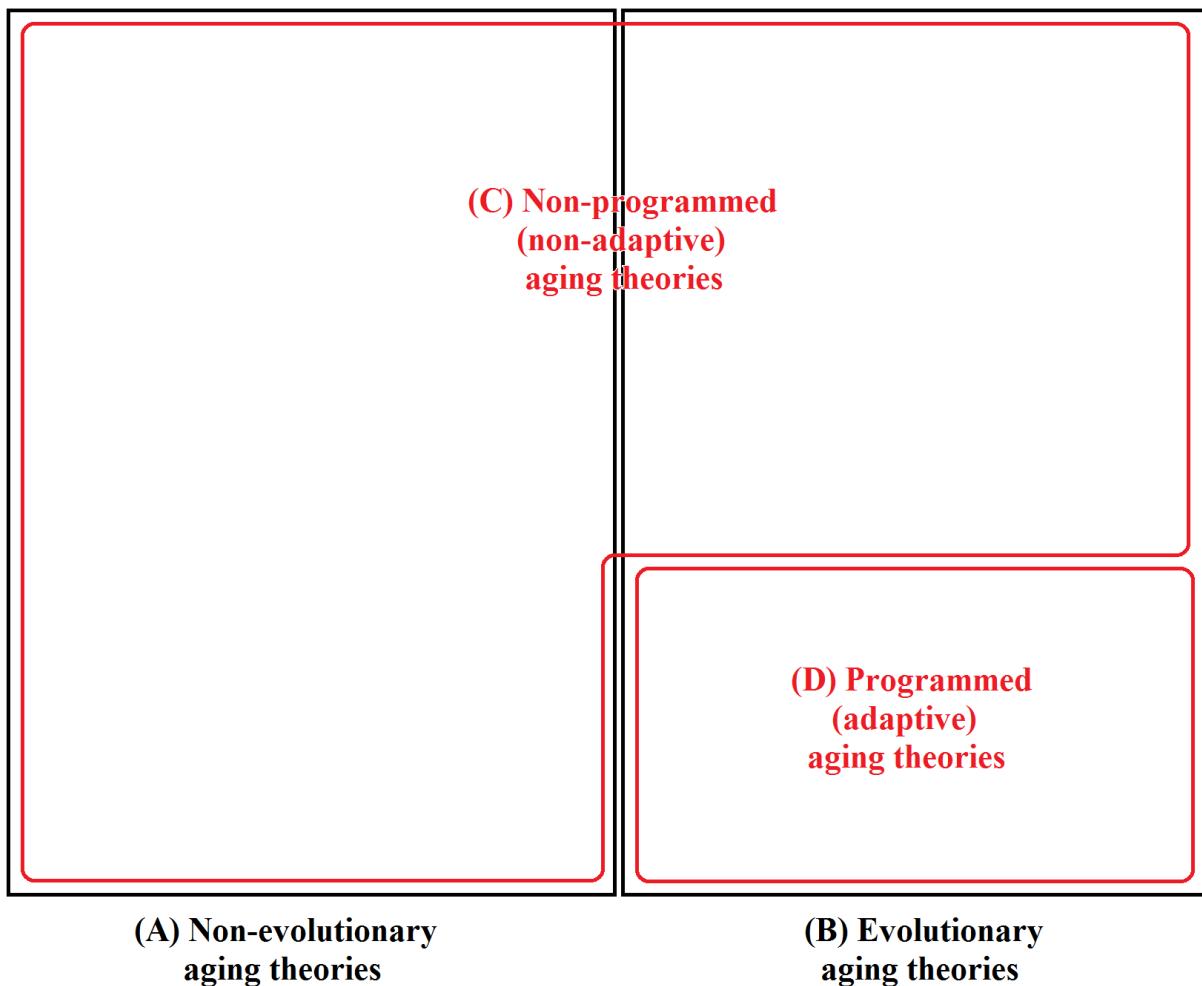


Figure 1.28 – Schematic classification of aging theories.

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