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Non-programmed Versus Programmed Aging Paradigm

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Abstract: There are two opposite paradigms to explain aging, here precisely defined as "age-related progressive mortality increase, *i.e.* fitness decline, in the wild". The first maintains that natural selection is unable to maintain fitness as age increases. The second asserts that, in particular ecological conditions, natural selection favors specific mechanisms for limiting the lifespan. The predictions derived from the two paradigms are quite different and often opposing. A series of empirical data and certain theoretical considerations (non-universality of aging; great inter-specific variation of aging rates; effects of caloric restriction on lifespan; damage of aging for the senescing individual but its advantage in terms of supra-individual selection; existence of fitness decline in the wild; proportion of deaths due to intrinsic mortality inversely related to extrinsic mortality, when various species are compared; impossibility of explaining the age-related fitness decline as a consequence of genes that are harmful at a certain age; age-related progressive decline of cell turnover capacities; on/off cell senescence; gradual cell senescence) are compared with the predictions of the two paradigms and their compatibility with each paradigm is considered. The result is that the above-mentioned empirical data and theoretical considerations strongly contradict and falsify in many ways all theories belonging to the first paradigm. On the contrary, they are consistent or compatible with the predictions of the second paradigm.

Keywords: Programmed aging, non-programmed aging, supra-individual selection, phenoptosis.

INTRODUCTION

Aging, here defined as "increasing mortality with increasing chronological age in populations in the wild" [1], alias "age-related progressive mortality increase, *i.e*. fitness decline, in the wild", is a phenomenon that is interpreted in two completely opposite ways [2].

The first, here referred to as the "old paradigm", sees aging as due to a variety of damaging factors that, with the passage of time, progressively undermine organism efficiency. Harmful actions are counteracted by natural selection, but this is sufficient only in part, and to a decreasing extent, at older ages. For some hypotheses, natural selection is restrained by pleiotropic genes or by physiological / biochemical contrasting demands.

The second, here referred to as the "new paradigm", sees the gradual decline of vital functions as a genetically programmed phenomenon, *i.e*. something that is determined and shaped by natural selection because it is advantageous in particular ecological conditions.

The empirical evidence in support of or against the two opposite paradigms has already been discussed previously [2]. Here, I wish to update and widen the discussion in the light of evidence that has subsequently come to light.

In this work, for the old paradigm, the main hypotheses, or category of hypotheses, will be considered:

- *Damage Accumulation hypotheses*. Aging is caused by the accumulation of damage of various kinds. The older hypotheses interpreted aging as caused by mechanical wear or by various types of biochemical damage and/or tissue degenerations, *e.g.* "wear and tear" without further specifications, mechanochemical deteriorations in cell colloids, changes in specific organs or tissues (nervous / endocrine / vascular / connective, *etc*.), accumulation of toxic substances produced by intestinal bacteria, accumulation of various metabolites, effect of cosmic rays, *etc*. [3].

The newer ones explain aging as a consequence of the accumulation of chemical damage due to DNA transcription errors [4], or as caused by oxidative effects of free radicals on the whole body [5-8], on the mitochondria [9-12] or on the DNA [4, 13].

- *Cessation of Somatic Growth hypothesis*. For organisms with a fixed growth, *i.e*. growth which ends when a determinate size has been attained, senescence starts when the growth of new tissues stops. Conversely, for species where the growth is without limits, as for many lower vertebrates, there is no age-related fitness decline [14-19].

- *Mutation Accumulation hypothesis*. Aging is due to the combined effect of many harmful genes that act late in life and are insufficiently removed by natural selection [20-24].

- *Antagonistic Pleiotropy hypothesis*. Aging is caused by genes that are both advantageous in the young or adult stage and disadvantageous in the older ages, and are, therefore, only partially counteracted by natural selection [25, 26].

- *Disposable Soma hypothesis.* Physiological and/or biochemical restrictions limit and hamper the maintenance of an optimal efficiency of maintenance systems at advanced ages. The body, in the allocation of poorly defined limited

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resources, must choose between higher reproductive capacity and a greater efficiency of maintenance systems. Therefore, the limited resources jeopardize the preservation of an optimum efficiency at advanced ages [27, 28].

- *Quasi-Programmed Aging hypothesis* [29]. For this theory, a variation of the Disposable Soma hypothesis: "nature blindly selects for short-term benefits of robust developmental growth ... aging is a wasteful and aimless continuation of developmental growth" [30].

As regards the new paradigm:

- The concept that aging has the hallmarks of an adaptation, *i.e*. something determined and modulated by natural selection, has been underlined by various Authors [31-34]. Skulachev coined [31] the pregnant neologism "phenoptosis" to define the vast and well-known [35] group of phenomena in which an individual sacrifices itself or close relatives by means of mechanisms favored by natural selection at a supra-individual level [31, 36, 37].

- It was Wallace, the co-discoverer of evolution by natural selection, who, in 1865-1879, proposed that death by aging was programmed [38]. In 1889, Weissmann, albeit without a clear exposition or sound proof, hinted that aging was beneficial because the death of old individuals was evolutionarily useful, liberating space for the next generation [39, 40]. Moreover, as regards the mechanisms causing aging, he hinted that cell turnover slackened or stopped in the older ages and this determined a loss of functionality for the organs and consequently fitness decline [40]. He later disowned these revolutionary ideas however [40, 41].

- In 1988 (anticipated in 1983 by a non-peer reviewed book [42]), a theory was put forward, justifying aging as adaptive in terms of kin selection, in spatially structured populations [1]. This hypothesis, which for the first time predicted an inverse relation between extrinsic mortality and the proportion of senescent deaths, was later reaffirmed [2, 43-45].

- Other theories underlining an evolutionary advantage for programmed death in spatially structured populations were put forward in 2004 and later on [46-48].

- In the context of aging interpreted as a programmed phenomenon favored by natural selection, the damage induced by mitochondrial ROS was seen as pivotal mechanism [38, 49, 50].

- Another theory, which follows Weismann's insight, maintains that aging is favored by natural selection in that it increases the speed of evolution, or evolvability [51, 52].

- In 2009, aging was explained as an adaptation to limit the spread of diseases, by analogy with Red Queen hypothesis on the adaptive meaning of sex [53].

- In 2008, a number of logical common predictions for all aging programmed hypotheses were underlined: A) the existence of species without an age-related increase of mortality; B) in a comparison of different species, an inverse relation between extrinsic mortality and the proportion of senescent deaths; C) the existence of specific aging-causing, genetically determined and modulated mechanisms. Moreover, it was stressed that: (A) would be hardly justified by many non-programmed aging theories; (B) and (C) were in total contrast with them [2].

DISCUSSION

In this section, I will consider a series of theoretical arguments and documented phenomena. Each of them will be weighed against the predictions of the two paradigms, and their compatibility or incompatibility with both paradigms will be examined.

1). Non-universality of Aging

Evidence: In his authoritative textbook, Finch reports, in the wild, for many species (including vascular plants, invertebrates and vertebrates) "Indeterminate Lifespans and Negligible Senescence", *i.e*. a life table without any age-related increase of mortality [35]. In some cases, in connection with an age-related increase in body size, which reduces the risk of death due to predation by other species, the mortality rate even decreases at older ages [54].

Predictions of old paradigm theories: According to the various theories of the old paradigm, aging should be present in all species in which the hypothesized causes are present. The exceptions should be precisely explained, in particular in terms of the correlation between the absence/presence of aging with the absence/presence of the hypothesized cause. The data do not seem to justify the numerous documented exceptions.

As regards the many non-evolutionary older aging hypotheses based on damage accumulation assumptions, it is sufficient to consult the classical documented review of Comfort [3]: the absence of age-related decline shown by many species in the wild is not at all justified or considered by these theories. An exception is the group of theories that explain aging as caused by the cessation of somatic growth. Bidder pointed out that, for many lower vertebrates, there was no age-related mortality increase and suggested that there was "some mechanism to stop natural growth so soon as specific size is reached. This mechanism may be called the regulator ... senescence is the result of the continued action of the regulator after growth is stopped" [17].

As regards "newer" hypotheses, at least for those claiming to fall within evolutionary dynamics, the insufficient investigation of the non-universality of aging and the lack of plausible explanations for it have already been pointed out by others: "The possibility of negligible senescence has not been widely discussed, and may be in conflict with mathematical deductions from population genetics theory" [55].

Predictions of new paradigm theories: According to the new paradigm, when the ecological conditions for the proposed advantage of aging are absent, natural selection always favors individuals with better fitness up until ages when, in the wild, the fraction of surviving individuals is so small as to render selection ineffective. Therefore, in absence of particular selective circumstances favoring life restraints, the default condition is that of non-aging, *i.e.* fitness must not show an age-related decline at ages existing in the wild.

On the other hand, a lifespan with programmed limits (*i.e*. genetically determined and controlled, or influenced

according to specific periods, or affected by particular events), within that broad category of phenomena, now generally referred to as "phenoptosis" [31], described by Finch and known to scientists for some time [35], is an evolved condition that requires specific evolutionary advantages, obviously in terms of supra-individual selection.

In short, cases of non-aging, which for the old paradigm constitute a large group of exceptions to the general rule of aging for all species (with strenuous and questionable attempts to justify them), conversely, for the new paradigm constitute the simplest condition, with many exceptions when particular ecological conditions favor this or that kind of phenoptosis.

2). Great Inter-specific Variation of Aging Rates

Evidence: Among the species whose individuals age, there is a wide variation in the rate of aging, even within the same phylum. For convenience of reasoning, I would stress that the rate of aging is inversely related to longevity, a parameter necessitating an exact definition, but which I will leave in its imprecise form for this type of reasoning.

Longevity: (A) is related to adult body weight in vertebrates [56-58]; (B) is related to adult brain weight in mammals (likely related to the ability of learning) [3, 58]; (C) does not appear inversely related to the rate of metabolism (*e.g.* birds have a high metabolic rate and often a long lifespan) [3].

Predictions of old paradigm theories: For each theory, the rate of aging should depend on the hypothesized cause for the phenomenon. For many non-evolutionary older theories there is clear contradiction or absence of relationship between aging rates and hypothesized causes [3].

Many of the newer evolutionary theories of the old paradigm could be compatible with (A) and (B) (greater body mass and greater capacity for learning imply stronger selective pressures in favor of a greater longevity), but do not seem compatible with (C) [3].

Predictions of new paradigm theories: Longevity must depend on the ecological conditions that favor aging. In addition, in the balance between (supra-individual) benefits and (individual) disadvantages of aging, both a greater body mass and a greater ability to learn increase the disadvantages of a shorter lifespan and therefore (A) and (B) are predicted and justified [1]. On the other hand, (C) is not predicted and is not necessary.

3). Effects of Caloric Restriction on Lifespan

Evidence: For a long time, it has been known that animals raised under conditions of caloric restriction (CR) have a greater longevity than animals with *ad libitum* feeding [59-61]. It is possible to interpret this evidence as a relation between CR and longevity increase or, alternatively, in the following ways: 1) It is an artificial phenomenon due to the overfeeding of control animals as the normal condition (*i.e.* that existing in the wild) is CR: "instead of comparing control animals with restricted animals, we are in fact comparing overfed animals with adequately fed ones, and, not surprisingly, the overfed ones die younger." [62]; 2) *Ad libitum* feeding is, in effect, hyperalimentation, which reduces longevity by favoring various pathological conditions [60, 63]; 3) The increase in longevity is only a laboratory artifact as CR in the wild would not have the effect of increasing lifespan [64].

Predictions of old paradigm theories: According to the Disposable Soma (DS) hypothesis, aging is due to the reduced availability of resources that forces an evolutionary choice that is whether to direct the resources towards reproduction or survival. By favoring reproduction, organism maintenance is reduced and aging is the consequence. It follows that a reduction in resources should lead to a reduction of longevity and vice versa. The effects of CR appear to be an increase, or at least the non-reduction, in longevity. Whatever the interpretation of the phenomenon, the empirical evidence does not seem to be compatible with the predictions of the DS hypothesis. A special feature of the DS theory has been put forward to solve this contradiction [65], but the proposed solution has been criticized as contradictory and insufficient [66].

Predictions of new paradigm theories: For the new paradigm, aging is not dependent on the greater or lesser availability of calories or of other metabolic limiting factors. Accordingly, the effects of CR are not in contradiction with the new paradigm, whatever the interpretation of these effects and the mechanisms that cause them. This does not exclude (on the contrary, it is predicted as likely) that ecological conditions to which a species is not adapted (*e.g.*: overfeeding) can be harmful and so may reduce longevity [67].

4). Damage of Aging for the Senescing Individual But its Advantage in Terms of Supra-individual Selection

Evidence: Natural observation shows an extraordinary number of phenomena in which an individual, or an immediate blood relative, is clearly sacrificed [35]. This proves beyond any doubt that natural selection can favour phenomena that are altogether unjustifiable in terms of strict individual selection.

Predictions of old paradigm theories: Authoritative supporters of the old paradigm, in a prominent journal, maintained that it is unlikely that phenomena harmful to the individual might be favoured by natural selection: "any hypothetical 'accelerated ageing gene' would be disadvantageous to the individual. It is therefore difficult to see how genes for accelerated aging could be maintained in stable equilibrium, as individuals in whom the genes were inactivated by mutation would enjoy a selective advantage" [68]. More recently, this conviction has been confirmed: "The anomalous nature of ageing as a putative adaptation is that it is bad for the individual in which the process is exhibited. An animal that grows to maturity and thereafter reproduces indefinitely has, other things being equal, a greater Darwinian fitness than one that grows to maturity and then survives and reproduces for only a fixed period of time." [69].

Predictions of new paradigm theories: Phenomena in which an individual sacrifices himself, or a direct blood relative, though widely known and described long ago [35], have only in recent times been defined under the unifying term

"phenoptosis" [31], with the explicit statement that these phenomena are genetically determined, and harmful to the individual concerned (or to direct blood relatives [37]). The new paradigm argues that aging is one among many types of phenoptotic phenomena ("slow phenoptosis" [70]), and therefore must necessarily be explained in terms of supra-individual selection [37]. The erroneous exclusion of the possibility that a character may be favored by natural selection because it is harmful at the individual level implies a restrictive and totally unacceptable conception of the mechanisms of natural selection [37, 71].

5) Existence of Fitness Decline in Wild Conditions

Evidence: For many animal species, there is a well-documented age-related increase in mortality at ages existing in the wild [72, 73]. As an example, Fig. (**1**) shows the life table and the mortality of the lion (*Panthera leo*) in natural conditions.

For our species, we have the data from the study of a human population (Ache of Paraguay) under natural conditions. This study shows that the fractions of surviving individuals at the ages of 65, 70 and 75 years, were 27%, 20% and 12%, respectively. Excluding individuals who died before they were twenty years old, the survivors at ages 65, 70 and 75 years, were 42%, 32% and 18%, respectively (see Fig. **2**) [74].

Predictions of old paradigm theories: In a 2000 Nature paper, influential supporters of the old paradigm, maintained the impossibility of an evolutionary advantage of any kind in aging because: "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" [68].

The concept has been reaffirmed over subsequent years: "Data on age-related mortality patterns in wild animal populations reveal that, in many species, individuals rarely survive to ages when senescent deterioration becomes apparent ..." [75]; "senescence-associated increases in age-related mortality are far from ubiquitous, and ..., even where they are observed, they contribute only to a relatively small fraction of deaths within the population, ..." [69].

Predictions of new paradigm theories: Thirteen years later, one of the Authors of the 2000 Nature paper [68], along with other Authors, says and documents the opposite: "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" [73].

In any case, the aforementioned objection regarding the absence of aging in the wild could be coherent within the restricted conception of aging erroneously limited to the existence of individuals with extreme functional decay, that is to say with levels of fitness reduced to arbitrarily established minimal values, which - by definition - are incompatible with survival. But, aging has been defined as the age-related progressive decay of functions and therefore cannot be identified with the extreme outcome of this decay.

Empirical data show that mortality increase (*i.e.* fitness decline) is well documented in the wild, and therefore is strongly influenced (*i.e.*, opposed or favored) by natural selection. Moreover, if we limit the discussion to our own species, in wild conditions the fractions of individuals in advanced stages of senescence are certainly remarkable, and this is another reason for which the concept of an *a priori* ineffectiveness of selection on aging is unacceptable.

6) Proportion of Deaths due to Intrinsic Mortality Inversely Related to Extrinsic Mortality, In a Comparison of Species

Evidence: For species that demonstrate age-related mortality increase (*i.e.* aging) in wild conditions, an inverse relation between extrinsic (or environmental) mortality and the proportion of deaths due to the age-related mortality increase has been well documented [72]. This relationship is confirmed by the inclusion of data from a human population studied in wild conditions [45].

Predictions of old paradigm theories: A direct relationship is plainly predicted: "The principal determinant in the evolution of longevity is predicted to be the level of extrinsic

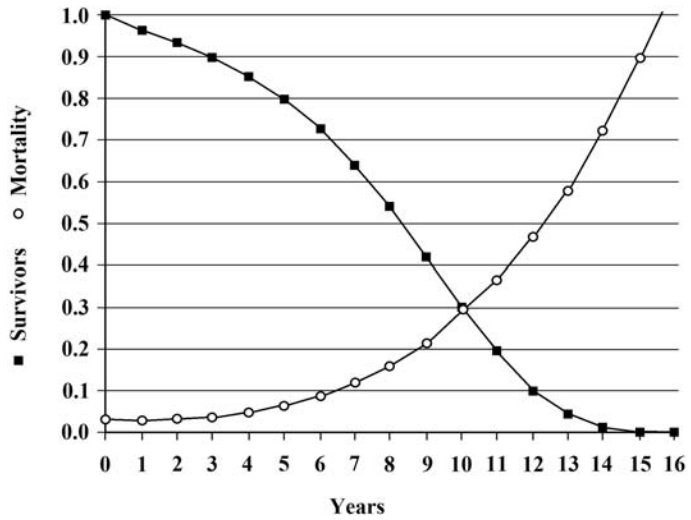

Fig. (1). Life table and mortality of *Panthera leo* in the wild (Data from Ricklefs [72]).

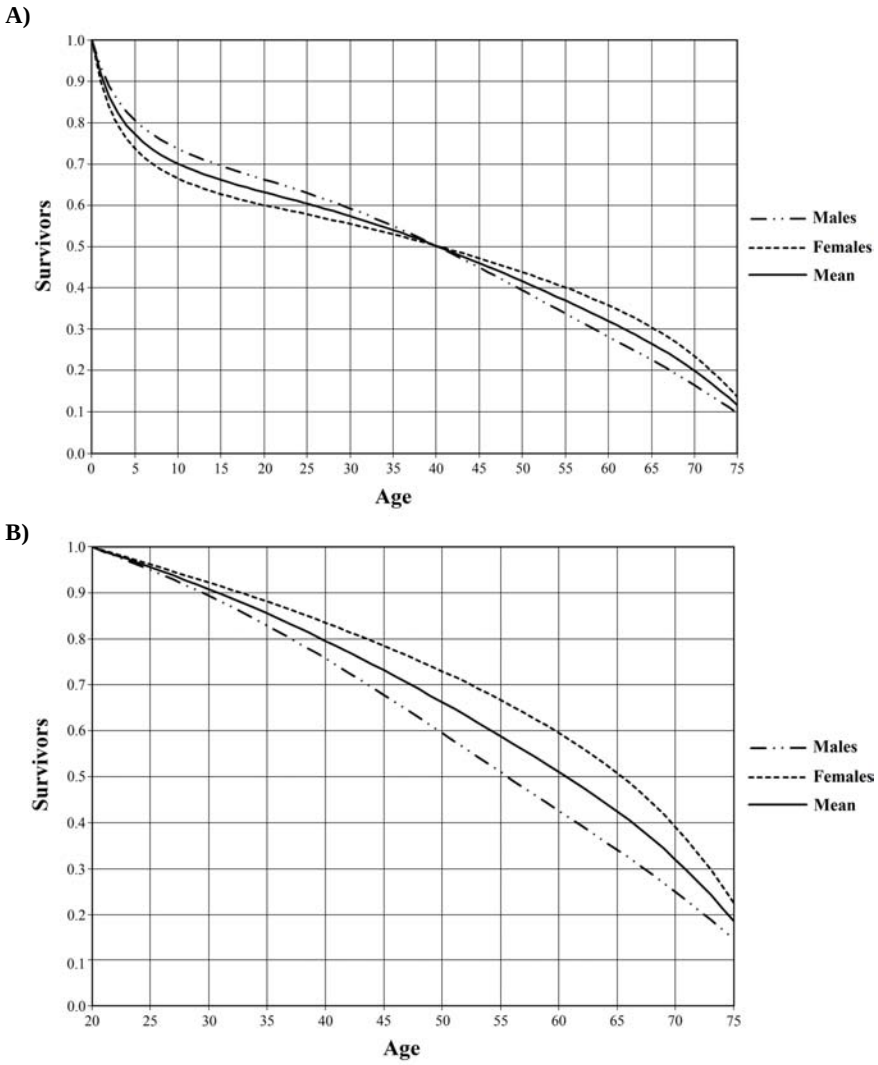

Fig. (2). Life table of *Homo sapiens* in wild conditions: **A**) whole population; **B**) limited to 20 years old survivors.
*Data from Ache population (Paraguay) [74].

mortality. If this level is high, life expectancy in the wild is short, the force of selection attenuates fast, deleterious gene effects accumulate at earlier ages, and there is little selection for a high level of somatic maintenance. Consequently, the organism is predicted to be short lived even when studied in a protected environment. Conversely, if the level of extrinsic mortality is low, selection is predicted to postpone deleterious gene effects and to direct greater investment in building and maintaining a durable soma" [68]. The contradiction between old paradigm hypotheses and the above-mentioned inverse relationship observed is clearly stated by Ricklefs, who, after reporting his data - a fatal blow against ingrained beliefs -, makes a feeble attempt at saving the DS hypothesis only [72].

Predictions of new paradigm theories: If aging is a programmed phenomenon, a paradoxical inverse relationship was predicted long ago [1, 42], well before Ricklefs' data [72] were published. This inverse relationship is also predicted by a model that shows aging to be advantageous in spatially structured populations [48]. It has been stressed that this inverse relation is implicitly a general prediction of programmed aging theories and that there is a clear contradiction with the predictions of non-programmed aging hypotheses: "adaptive hypothesis ... appears indispensable to explain the observed inverse correlation between extrinsic mortality and the proportion of deaths due to intrinsic mortality" [2]; "this complementary relationship between background death and evolved senescence is characteristic of adaptive theories of aging. A high background death rate leads to a *longer* evolved life span. This contrasts with classical theories, in which a high background death rate leads to a *shorter* evolved life span." [48]. However, no explanation compatible with old paradigm theories has been proposed.

7) Impossibility of Explaining Age-related Fitness Decline as a Consequence of Genes that are Harmful at a Certain Age

Evidence: This argument has already been discussed elsewhere [1], but it is useful and necessary to reassert and better expound it in this work, as it has never been disproved and is essential for the acceptability of the Mutation Accumulation (MA) hypothesis.

Let us consider a harmful gene (C), which reduces fitness by a value *s*, and its neutral allele (C'). If *v* is the mutation frequency of C' in C, and the frequency of the reverse mutation is considered, for the sake of simplicity, to be insignificant, it is possible to calculate the equilibrium frequency between the new mutations C' -> C and the elimination of C by natural selection. It is also possible to calculate the frequency of the phenotypic expression of the gene (P_e) both in the case that C is recessive:

$$P_e = v/s \quad (1)$$

and in the case that C is dominant:

$$P_e \approx v/s \quad (2)$$

The achievement of these formulas is explained in detail elsewhere [67].

By defining a "t-gene" as a hypothetical gene that is harmful, by a value *s*, at time t and neutral in the preceding ages, as a t-gene damages only the fraction of survivors at time t (Y_t), natural selection lowers its frequency in function of ($s\ Y_t$) and the formulas (1) and (2) become:

$$P_e \approx v/(s\ Y_t) \quad (3)$$

Now, let us consider a population with a constant mortality at each age (*i.e.*, a non-aging population) and verify whether the action of a considerable number of t-genes may determine a curve similar to that of a species with an age-related increase in mortality.

The base curve of the population is given by the equation:

$$Y_{t+1} = Y_t\ (1 - \lambda) \quad (4)$$

where: Y_x = survivors at time x; λ = death-rate.

Now, if we suppose m t-genes acting at time t, as many genes at time t+1, and so on, each with harm equal to s (for the sake of calculation simplicity assumed to be equal for all t-genes), the survivors at any time t+1 will be:

$$Y_{t+1} = Y_t\ (1 - \lambda - m\ s\ P_e) \approx Y_t\ (1 - \lambda - m\ v/Y_t) \quad (5)$$

The equation (5) does not include the value of *s*, which is therefore irrelevant, and, as the value of *v* is assumed to be small, the decrease in Y at each unit of time will be sensible only when the value of Y_t is small.

Fig. (**3**) shows a hypothetical life table with a constant mortality and the modifications caused by a large number of hypothetical t-genes. Fig. (**4**) shows: A) part of the life table of a species (*Panthera leo*) studied in natural conditions; B) the same life table without the increase in mortality due to intrinsic mortality and thus with the constant extrinsic mortality only; C) curve B plus the effects of a large number of hypothetical t-genes. In both figures, it is evident that the effects of the hypothetical t-genes do not cause curves which are comparable to that of a species that ages.

Predictions of old paradigm theories: For the MA hypothesis, aging would be caused by the cumulative effects of many t-genes.

Predictions of new paradigm theories: The argument proposed by the MA hypothesis is totally unacceptable for ages existing in the wild and therefore cannot be considered a plausible explanation for aging. As an interesting corollary, natural selection - by definition - cannot delete a t-gene that would exert its action at ages not existing in the wild. It follows that a species that does not show any mortality increase in the wild, might under artificial conditions and at ages successive to those existing in the wild show an age-related mortality increase due to t-genes that cannot be eliminated by natural selection. This theoretical prediction, already formulated before [1], concerns a phenomenon that should be clearly distinguished from aging.

8) Age-related Progressive Decline of Cell Turnover Capacities

Evidence: In normal conditions, in vertebrates, cells die continuously as a result of various types of programmed cell death (PCD). The most studied type of PCD is apoptosis, first observed in hepatocytes [76], but well documented in many other organs and tissues [44]. Other types of PCD are

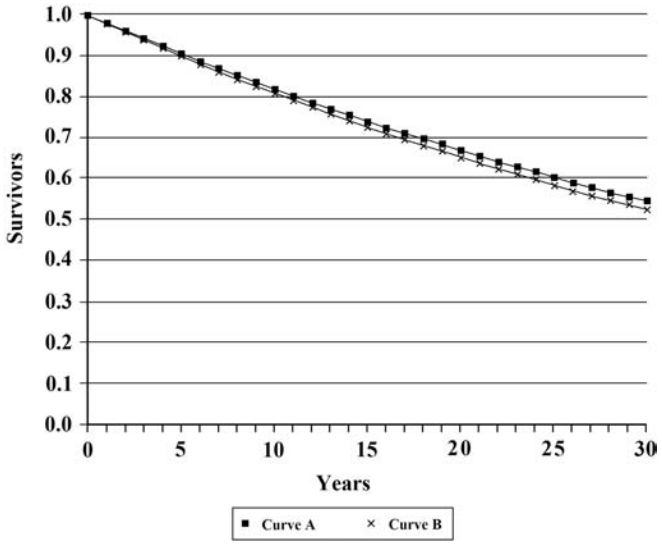

Fig. (3). Curve A: ideal life table obtained by formula 4, with λ = .02. Curve B: effects on curve A by a great number of t-genes, obtained by formula 5, with λ = .02; m= 1000; v= .000001.

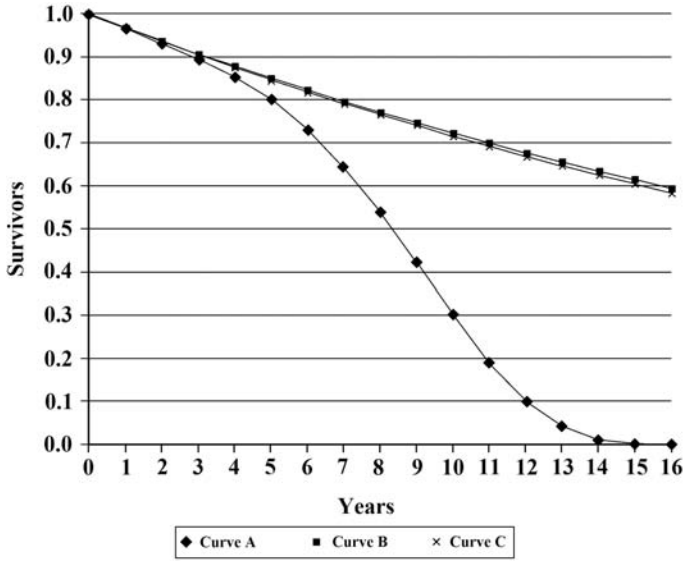

Fig. (4). Hypothetical effects of a great number of t-genes on the life table of a real species. Curve A, life table in the wild of *Panthera leo*, with mortality described by Weibull's equation ($m_t = m_0 + \alpha t^{\beta}$), using the values $m_0 = .032$; $\alpha = .000252$; $\beta = 3$; from Ricklefs [72]. Curve B, hypothetical, shows the same life table without the age-related increment of mortality, *i.e*. with a constant mortality ($m_0 = .032$). Curve C, hypothetical, shows the effects on curve B of a great number of t-genes (m= 1000; v= .000001;).

the keratinization of epidermis cells and subsequent detachment, the detachment of cells from mucosas, the phagocytosis of erythrocytes and of osteocytes, *etc*. Continuous cell death (50-70 billion / day [77]) is balanced by the continuous duplication of stem cells with rhythms that vary for each cell type and organ [78]. At the one extreme, cells of intestinal epithelium are renewed in 3-6 days [79], while heart myocytes in about 4.5 years [80] and osteocytes in about 10 years [79].

The few cell types that are not subject to cell turnover (*e.g.*, neurons of the central nervous system and retina photoreceptors) are strongly dependent on other cells that undergo turnover and that actively renew the critical parts of the cells without turnover [44].

However, cell turnover declines as one grows older due to known limitations in cell replication, first demonstrated by Hayflick in his seminal work [81].

Aging may be described as the result of the gradual decline of cell turnover, resulting in a progressive atrophy of all tissues and organs [44, 82], associated with the increase of the percentage of cells in cell senescence (on / off and gradual, s. below). In any case, cell turnover and its gradual decline are clearly subjected to a genetic regulation that is certainly very complex and sophisticated.

Predictions of old paradigm theories: Aging is not explained as a progressive slowdown in cell turnover. For the old paradigm, the limits in cell turnover, which are clearly genetically determined and modulated and determine an age-related fitness decline, cannot be explained as being caused by the accumulation of harmful effects and so must have a different acceptable explanation. The only proposed explanation is that these cell limits defend the organism from cancer [83, 84].

This justification, put forward and/or accepted by authoritative scholars, does not explain the existence of species without age-related fitness decline (species with negligible senescence), which show no age-related decline in telomerase activity and no age-related increase in cancer mortality [2]. Moreover, for our species studied in the wild, fitness decline – *i.e*. aging - kills almost all individuals before cancer cases become a detectable cause of death and it is unlikely that a defense against cancer may kill before the disease begins to be lethal [45]. Other strong objections to the above-mentioned justification for the limits in telomerase action, and consequently in cell turnover, have been underlined with clear conclusions: "The hypothesis that telomerase is restricted to achieve a net increase in lifespan *via* cancer prevention is certainly false. Were it not for the unthinkability of the alternative – programmed death – the theory would be dead in the water" [85].

Predictions of new paradigm theories: The new paradigm predicts and, indeed, absolutely requires aging to be genetically determined and regulated. Therefore, the above-mentioned phenomena, which gradually reduce fitness, are not in conflict with the new paradigm but rather are essential to its plausibility [2].

9) On/Off Cell Senescence

Evidence: Cells pass from a cycling state, in which they can duplicate, to a non-cycling state, where cells cannot duplicate, through the random activation of a mechanism with a probability inversely proportional to the reduction of telomere length [86].

The inactivation of replication capacities is part of a specific complex mechanism, cell senescence, which is characterized by predictable and stereotyped modifications and is considered a "fundamental cellular program" [87].

In the senescent state, cells are characterized by complex alterations of transcriptome, with many cell functions compromised, including the cell secretions in the intercellular

matrix and the consequent damage to other cells and to the functionality of the tissues / organs of which the cells are part [88]. Among other things, cell senescence results in a lower resistance to oxidative substances and in an accumulation of oxidative damage. But it is worth pointing out that the damage caused by oxidation is a consequence and not the cause of cell senescence [89]. Moreover, it is well established that cell senescence and all its manifestations, including oxidative damage, are totally reversible by activating the enzyme telomerase [90-93].

Predictions of old paradigm theories: For the old paradigm, aging is caused by the accumulation of various types of damage in many locations (depending on the various assumptions of the hypotheses). The fact that a cell changes from the condition of cycling state / non-senescence (no damage evident) to non-cycling / senescent state (damage of many types) as a consequence of the activation of a specific program is completely unexpected. Equally unforeseen is that this program is completely reversible with the total disappearance of the damage caused by cell senescence and the perfect reactivation of replication capacities. Moreover, cell senescence is activated in somatic cells and not in germline cells and this means that the mechanism is not an inevitable feature of living cells or an inevitable consequence of replications, but a sophisticated mechanism that cannot be the consequence of damage accumulation and that requires specific selective advantages to justify its existence.

These phenomena are in clear and complete contradiction with the predictions of old paradigm theories. Cell senescence absolutely needs a justification, other than that of its unlikely attributed anticancer powers, in order to nullify this contradiction.

Predictions of new paradigm theories: The new paradigm predicts and, indeed, absolutely requires aging to be genetically determined and regulated. Therefore, the above-mentioned phenomena, which gradually reduce fitness, are not in conflict with the new paradigm but rather are essential to its plausibility.

Some of these concepts are illustrated in Fig. (**5**).

10) Gradual Cell Senescence

Evidence: In yeast (*Saccharomyces cerevisiae*), telomerase is always active and telomere length does not decrease with duplications [94, 95]. Moreover, there is an asymmetric division between mother and daughter cells: while the mother lineage may continue only for a limited number of generations and there is a progressive decline in the ability to withstand stress [96], daughter ("budding") yeast cells divide indefinitely [97].

In mother cells, extrachromosomal ribosomal DNA circles (ERCs) accumulate at each duplication [98], "several lines of evidence suggest that accumulation of ERCs is one determinant of life span", and, in proportion to the number of duplications, increasing metabolic alterations, definable as cell senescence, are evident [99].

These alterations are a likely consequence of ERCs accumulation which interferes with gene expression of critical parts of subtelomeric DNA. As a matter of fact, yeast dna2-1 mutants, with abnormalities in DNA duplication and thus increased rates of ERCs accumulation, show precocious alterations of gene expression. In particular, transcriptome of older wild-type individuals of mother lineage are similar to those of young mother individuals of dna2-1 mutants [99].

In yeast, tlc1Δ mutants, which are telomerase-deficient mutants, both mother and daughter cells show telomere shortening and individuals of daughter cell lineages, which have no ERCs accumulation, have a transcriptome similar to that of older wild-type individuals of mother lineage, and of

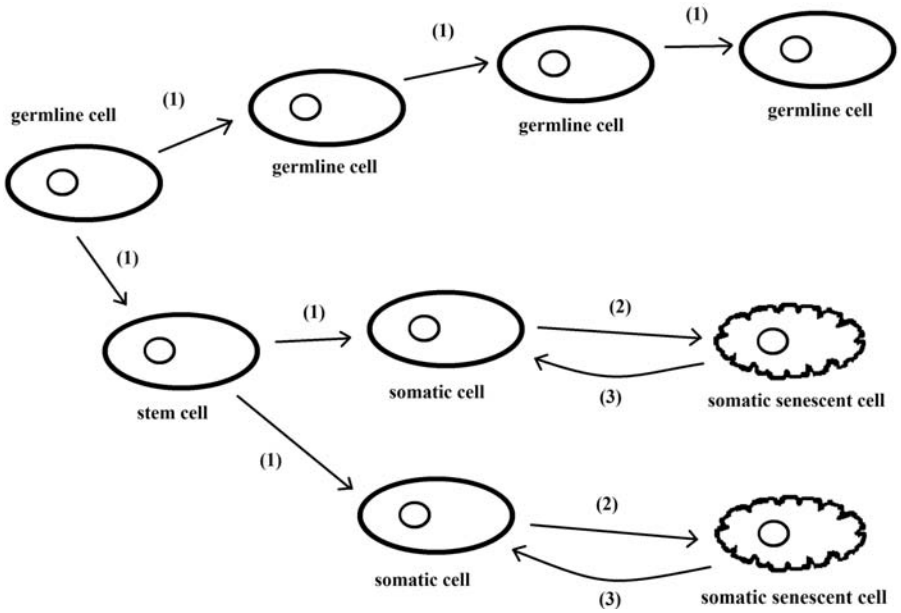

Fig. (5). Germline and stem cells duplicate (1) and do not change into senescent cells. On the contrary, somatic cells are subject to cell senescence phenomenon (2). This difference is not easily explainable if cell senescence is caused by damaging factors. Analogously, the complete reversibility of cell senescence (3), by activation of telomerase, is explainable only if cell senescence is a programmed phenomenon. This evidence is in clear contrast with the old paradigm.

individuals of dna2-1 mutants [99]. It is possible that in tlc1Δ mutants, telomere shortening causes the sliding of a telomere heterochromatin hood which interferes with subtelomeric DNA, while in wild-type yeast subtelomeric DNA is somehow repressed by ERCs.

In multicellular eukaryotic organisms, in proportion to the number of duplications there is an increasing probability of replicative senescence and an increasing alteration in the expression of many genes, *i.e*. an alteration of the transcriptome, which compromises overall cell functionality and has deleterious consequences on the extracellular matrix and on other cells that are physiologically interdependent. All this is certainly in relation to the relative shortening of telomere (Fossel's "cell senescence limited model") [89].

"One model of telomere-gene expression linkage is an altered chromosomal structure (Ferguson *et al*., 1991), such as a heterochromatin 'hood' that covers the telomere and a variable length of the subtelomeric chromosome (Fossel, 1996; Villeponteau, 1997; Wright *et al*., 1999). As the telomere shortens, the hood slides further down the chromosome (the heterochromatin hood remains invariant in size and simply moves with the shortening terminus) ... the result is an alteration of transcription from portions of the chromosome immediately adjacent to the telomeric complex, usually causing transcriptional silencing, although the control is doubtless more complex than merely telomere effect through propinquity (Aparicio and Gottschling, 1994; Singer *et al*., 1998; Stevenson and Gottschling, 1999). These silenced genes may in turn modulate other, more distant genes (or sets of genes). There is some direct evidence for such modulation in the subtelomere ..." [89].

Recent results confirm the influence of telomere length on subtelomeric DNA: "Our results demonstrate that the expression of a subset of subtelomeric genes is dependent on the length of telomeres and that widespread changes in gene expression are induced by telomere shortening long before telomeres become rate-limiting for division or before short telomeres initiate DNA damage signaling. These changes include up-regulation and down-regulation of gene expression levels" [100].

In short, in yeast and in multicellular eukaryotic organisms, subtelomeric DNA is of pivotal importance for overall cell functionality and is vulnerable to inactivation as a consequence of telomere shortening or of ERCs accumulation around the telomere. Excluding the possibility of an absurd evolutionary illogicality, this positional vulnerability must be somehow explained in terms of natural selection.

This evidence and the deduced concepts are illustrated in Fig. (**6**).

Predictions of old paradigm theories: If aging is opposed by natural selection, it is quite illogical – or rather

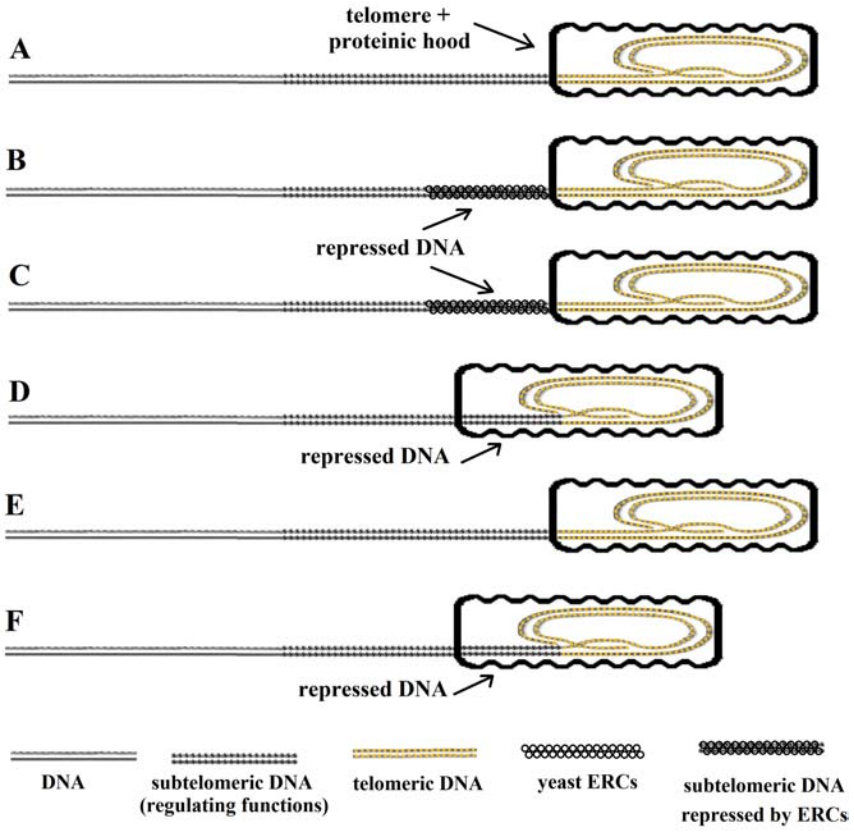

Fig. (6). A) yeast, normal stock, daughter lineage; **B**) yeast, normal stock, old individuals of mother lineage; **C**) yeast, dna2-1 mutants, young individuals of mother lineage; **D**) yeast, tlc1Δ mutants, daughter lineage; **E**) multicellular eukaryotes, normal stock, germinal line; **F**) multicellular eukaryotes, normal stock, somatic line. In A and E, telomeres are not shortened and subtelomeric DNA is not repressed. In B and C, subtelomeric DNA is repressed by the accumulated ERCs. In D and F, telomere are shortened and the subtelomeric DNA is repressed by the proteinic hood.

unlikely - that delicate parts of the DNA with general regulatory functions, will be placed in the position most exposed to the consequences of telomere shortening, as the sliding of the telomeric hood on the subtelomeric segment (or the ERCs accumulation, in yeast) dysregulates genes that are critical for cell functions.

Predictions of new paradigm theories: The gradual impairment of cellular functions in relation to telomere shortening, or to ERCs accumulation in yeast, which are phenomena based on genetically determined mechanisms, is perfectly compatible with the new paradigm and indeed represents a further element of sophistication of the system. As regards the thesis that this could be part of a hypothetical general defense against cancer, see what has been said in the previous subsection. Moreover, in unicellular species, such as yeast, cancer is by definition impossible, but in these species, which show aging in the mother lineage cells, there is a similar mechanism in which the vulnerability of the subtelomeric DNA segment, which is crucial for the general functioning of the cell, has not been countered by natural selection. Incredibly, although the common ancestors of mammals and yeast date back over 600 million years ago, (i) the vulnerability of the subtelomeric segment, (ii) its crucial importance for the functionality of the entire cell, (iii) the progressive damage to this segment in relation to cell doublings (in the mother lineage cells for the yeast and in the cells in which telomerase is not active for mammals) are highly conserved features, although they are clearly harmful in individual terms.

CONCLUSION

1 - The absence of an age-related mortality increase in many species requires, for non-programmed aging hypotheses, specific justifications, which are inexistent (with the sole exception of the Cessation of Somatic Growth hypothesis). This does not exclude the possibility that specific explanations for each case may exist, but until they are found, the absence thereof should be considered as a point against non-programmed aging hypotheses. The Cessation of Somatic Growth (CSG) hypothesis is an exception, as it justifies non-aging conditions in species with continuous somatic growth.

2 - In a comparison of the species, in particular within the same phylum, the great variability in aging rates should be in direct relation to the strength of the hypothesized causes for aging in the various hypotheses. But, in many cases, the theories of the old paradigm do not demonstrate a direct relationship between aging rates and the hypothetical causes and, furthermore, in some cases we find the opposite relationship [3]. In this case too, the CSG hypothesis is an exception, as it could justify aging rate variety as related to growth differences.

3 - The effects of caloric restriction on longevity, that is to say, its observed increase or at least non-increase, are in clear contrast with the predictions of the Disposable Soma hypothesis.

4, 5 - Old paradigm theories are based on two assumptions which are totally groundless: A) aging does not exist in natural conditions; B) a character that is disadvantageous in individual terms cannot be favored by natural selection. These assumptions would result in the impossibility of a programmed aging theory and in the absolute necessity for an explanation for aging to fall within the old paradigm. As the two concepts are blatantly wrong, it follows that an age-related fitness decline cannot be explained without some form of evolutionary advantage. Therefore, the two alleged arguments against the new paradigm and in support of the old paradigm become the opposite, *i.e*. arguments against the old paradigm and in support of the new paradigm.

Among the older theories, the CSG hypothesis does not claim the absence of senescence in the wild and so it cannot be criticized on this point.

6 - The prediction of a direct relationship between extrinsic mortality rates and proportions of deaths due to aging is intrinsic to all old paradigm theories while the opposite is expected from new paradigm theories [2]. The evidence [72] is against the old paradigm and in support of the new one. Moreover, there is the complete lack of an explanation compatible with old paradigm theories, which seem to ignore or gloss over the topic.

7 - The existence of a strong, unrefuted, theoretical demonstration [1], against the seemingly indisputable theorem that aging is wholly, or at least partially, a consequence of natural selection that weakens as survivors decline with age, is an insuperable blow to the Mutation Accumulation hypothesis. There is, perhaps, a concealed awareness of this weakness which is the basis for the origin of the Antagonistic Pleiotropy and Disposable Soma hypotheses, the first of which assumes the existence of genes advantageous at lower ages and disadvantageous at higher ages, and the second which postulates insuperable limits in the availability of ill defined resources. The supporters of these two hypotheses fail to demonstrate the existence of pleiotropic genes or of limited resources. In addition, the above-mentioned hypotheses do not explain at all the great variability of aging rates in a comparison of species, meaning that there is probably an implicit assumption that pleiotropic genes and limiting factors are variable depending on the greater or lesser longevity (an *ad hoc* unacceptable hypothesis). However, it is necessary to stress that hypotheses based on postulates, or on multiple layers of postulates, cannot be considered scientific.

8, 9, 10 - Progressive decline in cell turnover capacities, on/off cell senescence and gradual senescence, while fully compatible and, indeed, necessary for the new paradigm, are totally incompatible with old paradigm theories, unless a sound justification of their existence, other than that of their being part of the aging mechanism, is put forward. The hypothesis that they are a general defense against cancer is untenable. Moreover, for gradual senescence, even the aforementioned explanation could not justify why DNA parts with fundamental regulatory effects on cell functions are localized in the subtelomeric portion, which is the most vulnerable in proportion to the number of replications. Besides, such localization is phylogenetically very old and is also present in unicellular species, in which cancer is impossible.

These considerations are summarized in Table **1**.

In short, old paradigm hypotheses prove to be entirely untenable and of historical value only, while the new para-

Table 1. Correspondence between empirical data / theoretical arguments and the various theories.

	DA	CSG	MA	AP	DS	QPA	New Paradigm
1) Non-universality of aging	No/-	Yes	No/-	No/-	No/-	No/-	Yes
2) Great inter-specific variation of aging rates	No/-	Yes	No/-	No/-	No/-	No/-	Yes
3) Effects of caloric restriction on lifespan	-	-	-	-	No	-	Yes
4) Damage of aging for the senescing individual but its advantage in terms of supra-individual selection	No	-	No	No	No	No	Yes
5) Existence of fitness decline in wild conditions	No	Yes	No	No	No	No	Yes
6) Proportion of deaths due to intrinsic mortality inversely proportional to extrinsic mortality, in a comparison of species	No	No	No	No	No	No	Yes
7) Impossibility of explaining age-related fitness decline as a consequence of genes that are harmful at a certain age	-	-	No	-	-	-	Yes
8) Age-related progressive decline of cell turnover capacities	No	No	No	No	No	No	Yes
9) On/off cell senescence	No	No	No	No	No	No	Yes
10) Gradual cell senescence	No	No	No	No	No	No	Yes

Abbreviations: DA = Damage Accumulation hyp.; CSG = Cessation of Somatic Growth hyp.; MA = Mutation Accumulation hyp.; AP = Antagonistic Pleiotropy hyp.; DS = Disposable Soma hyp.; QPA = Quasi-Programmed Aging hyp.; No = not explained or predicted by the hypothesis or in contrast with its predictions; - = irrelevant for accepting/rejecting the hypothesis; Yes = predicted by the hypothesis or compatible with it.

digm is clearly compatible with the empirical data and the theoretical arguments.

CONFLICT OF INTEREST

The author confirms that this article has no conflict of interest.

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PATIENT'S CONSENT

Declared None.

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