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Chapter 4

Prospects of a Longer Life Span beyond the Beneficial Effects of a Healthy Lifestyle

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Abstract

Life span is limited by the effects of diseases and ageing. For the aim of a longer life span, it is indispensable that a rational analysis of the primary causes of these phenomena is not limited to the description of their physio-pathological mechanisms. If Dobzhansky's statement that "nothing in biology makes sense, except in the light of evolution" is true, it appears logical to maintain that evolution theory must be the main tool for such analysis.

From an evolutionary point of view, diseases are the predictable consequence of: 1) defects in the maintenance and transmission of genetic information; 2) alterations of the ecological niche to which the species is adapted (in particular, for our species, due to civilisation); 3) interactions with other species (bacteria, viruses, fungi, protozoa, parasitic worms, etc.); and 4) conditions for which the species is not adapted.

Moreover, evolution theory allows the paradoxical prediction that, in particular ecological conditions, kin selection favours a progressive fitness decline, usually, in its more evident manifestations, referred to as ageing and that must not be classified as a disease. This decline is genetically determined and regulated and is obtained with a progressive limitation of cell turnover through a sophisticated modulation of the telomere-telomerase system.

A lifestyle compatible with the ecological niche to which our species is adapted and good medical treatment permit the attainment of the highest life span defined by the genetic program of our species (within the limits of individual genetic peculiarities) but

do not allow the overcoming of the maximal values of longevity defined by the same program.

To increase these values, it is indispensable to modify the genetic planning of ageing, with a different modulation of the telomere-telomerase system.

In principle, granted that this will be considered ethically acceptable, it is possible to propose a modification of that part of the genetic program that modulates ageing so that an unlimited survival is obtained, similar to the so-called “negligible senescence” observed for many animal and plant species.

A possible schedule to achieve this aim and the effects on human civilisation are outlined.

Premise

Disease is usually defined as an alteration of physiological conditions. If it is true that evolutionary mechanisms are indispensable for the full understanding of any biologic phenomenon [1], it is necessary to investigate if and how diseases and other phenomena causing suffering, disability and/or death are explainable and classifiable in evolutionary terms and whether from this approach useful indications may be deduced.

This question is the object of so-called Darwinian or evolutionary medicine [2,3,4,5,6,7], proposed in 1991 [2] but with some known forerunners [8].

In fact, the main concept of evolutionary medicine, the “discordance” between the conditions to which our species is adapted and actual conditions of life as a very important cause of disease, was already clearly expressed and well documented before the term “Darwinian medicine” was formulated [9].

Another forerunner [10] stated many of the concepts expressed by Williams and Nesse [2,3] with a substantial difference. For current evolutionary medicine, in accordance with prevalent gerontological ideas [11], ageing is the result of insufficient selection for a greater longevity and, in particular, of a trade-off between better somatic maintenance and reproduction capacity versus greater longevity [12]. Alternatively, it was proposed that mechanisms underlying ageing are favoured by kin selection, in particular ecological conditions [10,13], and therefore age-related fitness decline should be considered a physiological function and not a set of unrelated pathological conditions insufficiently countered by natural selection. This paradoxical and heretical different interpretation of ageing, which is in accordance with the general hypothesis of ageing as adaptive phenomenon [14,15,16,17,18,19,20], has been reaffirmed recently with the support of empirical evidence that disproves the classic interpretation [21,22]. Moreover, regarding the possibility of drastic modifications of human longevity, ageing considered as “a specific biological function rather than the result of a disorder in complex living systems” [15] allows totally new perspectives, based both on theoretical arguments and on the extraordinary advances in the understanding of the telomere-telomerase system, apoptosis, cell turnover and related arguments.

The Basic Question

Anatomy, physiology and behaviour characterising each species, ours included, are modelled and influenced by natural selection which has acted for innumerable generations. As natural selection improves fitness and reproduction capacity, a logical prediction is that individuals of a species should have the best fitness and reproduction capacity, with the exception of rare particular cases.

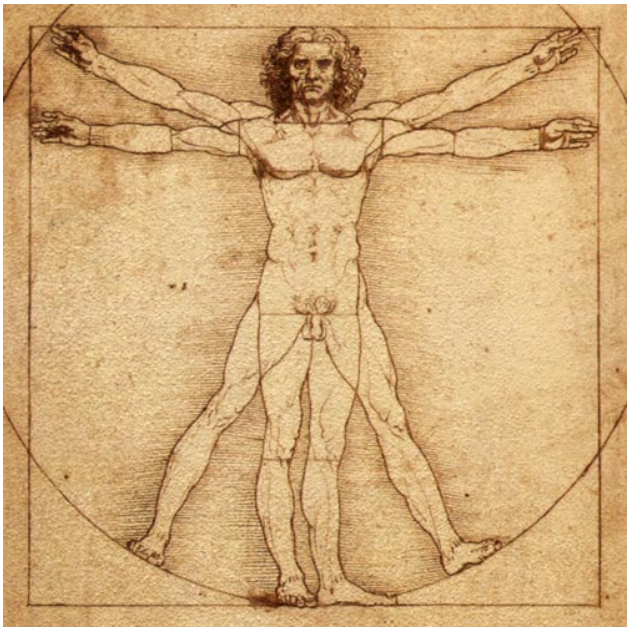
Yet, individuals of our species suffer from many diseases or other disabling conditions, and death is a common end to many of these conditions (Figure 1).

The incredible complexity and the amazing capacities of the eyes, the brain, the metabolic pathways and innumerable other characteristics of living beings are a marvellous fruit of natural selection, but diseases and other disabling conditions are a clear challenge for our confidence in the power of natural selection [3].

In short, is the evolutionary design of our species, although complex and admirable, a partial failure because we are afflicted by many imperfections and severe defects? Alternatively, are these imperfections and severe defects intrinsic to the evolutionary process?

This question is particularly important for the understanding of the causes of diseases that torment our species.

The problem is not a useless theoretical disquisition [23]: a rational answer to this question is the basis for the comprehension of the primary causes of diseases and similar conditions, for elaborating correct strategies to limit morbidity and mortality and for enhancing life span (mean duration of life) and longevity (the greatest duration of life).



(A)

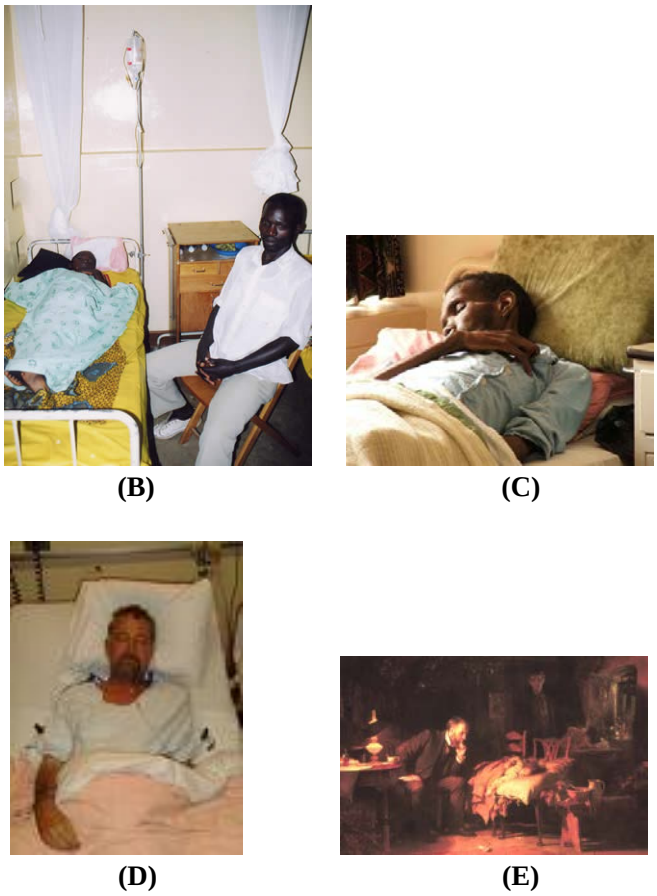


Figure 1. A) Vitruvian man (Leonardo da Vinci). This image could be the symbol of natural selection that shapes an organism without inappropriate imperfections. B) to E) Images illustrating some of the many conditions afflicting our species and that seem to indicate the failure of natural selection.

Evolutionary Classification of Diseases and Other Phenomena Causing Suffering, Disability and Death

1. Diseases Caused by Alterations of the Genotype

The preservation of genetic information and its transfer from a generation to the next is imperfect, a fact that is fundamental for the whole evolutionary theory as without genetic diversity selection would be impossible. Genetic information rules a sophisticated program that determines organism development and functions, both very complicated phenomena. A random modification in a very complex structure is, as more probable event if not neutral, an alteration that is a cause of dysfunction (Figure 2). Natural selection acts against the spreading of harmful alterations. Therefore, it is predictable that in a species there will be

many alterations of genetic information, each with a low frequency by effect of natural selection.

Figure 2. A random modification in a complex structure is a probable cause of breakdown.

The equilibrium frequency between the onset of new cases of genetic alterations and their elimination by natural selection is easily calculable. If the harmful gene C is recessive, its equilibrium frequency (C_e) will be:

$$C_e = \sqrt{-v/s} = \sqrt{v/[s]} \quad (1)$$

where v = mutation rate from an inactive allele (C'); -s = damage caused by C (the value is negative as C is harmful); [s] = absolute value of s (for the calculation of the formulas 1-7, see Appendix).

Using Hardy-Weinberg formula (CC + 2 CC' + C'C' = 1), the equilibrium frequency of the phenotype expressing the disadvantageous condition (P_e) will be:

$$P_e = C_e^2 = v/[s] \quad (2)$$

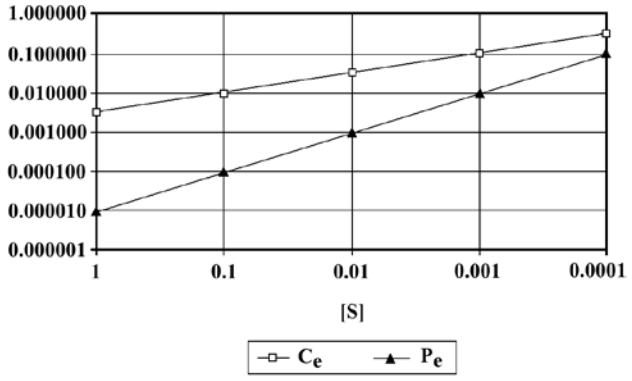
If C is dominant, its equilibrium frequency will be:

$$C_e = \frac{1 - \sqrt{1 - 3\,v/[s]}}{3} \approx 0.5\,v/[s] \quad (3)$$

and the equilibrium frequency of the phenotype expressing the disadvantageous condition (P_e) will be:

$$P_e = C_e^2 + 2\ C_e\ (1\text{-}C_e) = 2\ C_e - C_e^2\ \approx\ 2\ (0.5\ v/[s]) - (0.5\ v/[s])^2\ \approx\ v/[s] \qquad (4)$$

These equilibrium frequencies are illustrated in Figure 3.



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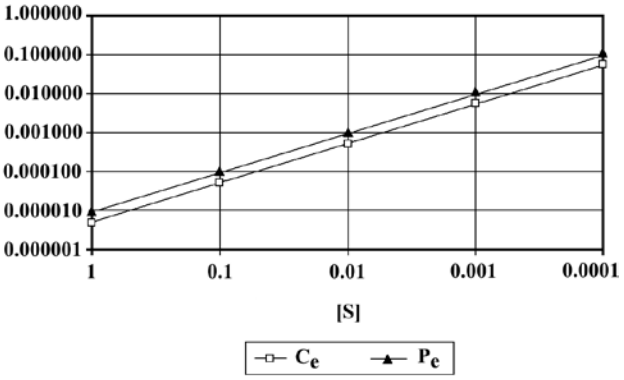


(B)

Figure 3. A) Equilibrium gene frequency (C_e) and phenotypic frequency (P_e) for a recessive harmful gene. B) Equilibrium gene frequency (C_e) and phenotypic frequency (P_e) for a dominant harmful gene.

For chromosome alterations, v can be interpreted as the frequency of the onset of a chromosome alteration and its equilibrium frequency, which coincides with its phenotypic frequency, is:

$$P_e = C_e = v/[s] \qquad (5)$$

as for a noxious gene in a haploid organism.

If n types of mutations, with a mean mutation rate v, can transform neutral alleles into C, the equilibrium phenotypic frequency of C will be:

$$P_e = n\,(v/[s]) \qquad (6)$$

These formulas mean that with small values of v (e.g., $v < 0.00001$), if [s] is not very small, the predicted frequency of a disease (P_e) caused by particular alterations of the genotype is very small, that is harmful alleles are constantly and efficaciously removed by natural selection.

This is not true in two cases.

1) If the value of [s] is very small, e.g., in the case that the harmful expression of the gene is at ages when only a few individuals survive and their remaining expectation of life and therefore their reproductive value is minimal, P_e will be not small. This is an argument of the "mutation accumulation" theory of ageing (see later).
2) If C is disadvantageous in the homozygous state ($s < 0$) and advantageous in the heterozygote state ($s' > 0$), its equilibrium frequency will be:

$$C_e = -\frac{2s'}{s - 4s'} = \frac{2s'}{[s] + 4s'} \qquad (7)$$

and it is easy to calculate the equilibrium frequencies of homozygous and heterozygote conditions (if $s > 0$ and $s' < 0$, $C_e=1$). The high frequency of some types of genetically determined anaemias (sickle cell anaemia, thalassaemia, G6PD deficiency, etc.), which are mild in the heterozygote state and deadly in the homozygous state, is explained by their advantage against malaria in the heterozygote state [8].

However, disregarding these particular cases, the theoretical prediction is that in a species there will be many diseases caused by alterations of the genotype, each with a very low frequency (greater when many different mutations alter the same gene or the same metabolic pathway) but with an overall frequency not small.

2. Diseases Caused by Alterations of the Ecological Niche

A modification of the ecological conditions to which a species is adapted, is a change in a very complex and ordinate system. Therefore, a modification of the ecological niche will be, as more probable event if not neutral, a cause of physiological dysfunctions (Figure 4).

Figure 4. A random modification in a very complex ordered sequence is a probable cause of disharmony.

Evolution is a slow process. If a species has been for a long time (thousands of generations) in a particular ecological niche (climatic conditions, behavioural and nutritional habits, relations with other species, etc.), the species should be considered as well adapted.

If the ecological niche changes, the adaptation to the new conditions may require times very long for the human standards, e.g., thousands of generations, which means 20,000-30,000 years for each thousand of generations.

From the origins to about 10,000 years ago, our species lived in Palaeolithic conditions (Stone Age) and, presumably, was well adapted to this "ancestral condition". With the Neolithic revolution, agriculture and breeding modified strongly our ecological niche. Afterwards, the massive urbanisation, the huge increase in demographic density, technological innovations, the industrial revolution, etc., have caused even greater changes.

Only a partial adaptation to the new conditions is documented or plausible. For example, adult Stone Age men were unable to digest fresh milk after being weaned and the greater part of modern men have the same inability except some populations in Europe, western India and sub-Saharan Africa that, having reared cattle from thousands of years, have acquired the capacity to digest fresh milk in adulthood [24].

The radical modification of our conditions of life has strikingly worsened the mean health of modern men in comparison with populations living in Stone Age-like conditions (hunter-gatherers or foragers). Some years ago, there were a few remaining populations with these lifestyle (e.g., some Australian aborigines, Hadza in Tanzania, !Kung of Botswana, Ache of Paraguay, Efè of the Democratic Republic of the Congo, and Agta of the Philippines [8]) and they showed almost no dental caries [25], hypertension, diabetes, obesity, cardiovascular

affections, cancer, psychological and emotional ailment [26], although more than 8% of the individuals exceeded 60 years of age [27].

Some examples of particular alterations of our ecological niche and the consequent diseases are listed in Table 1. A complete list with the discussion of the particular pathological mechanism for each disease would require a textbook.

Table 1.

Alterations of the ecological niche -> Diseases
Excessive ingestion of salt -> hypertension [9,28,29] (-> heart hypertrophy, congestive heart failure, arrhythmia and sudden death [30]) (Figure 5)
Excessive time spent focusing close up or in improper conditions of vision -> myopia [31] (up to 70–90% of a population affected [32,33]), refractive defects (myopia, astigmatism, hyperopia) [34]
Excessive ingestion of unsaturated fats, caloric foods, meat with high fat content -> obesity (->renal cell carcinoma [35], heart hypertrophy, congestive heart failure, arrhythmia and sudden death [30]) (Figure 6), type 2-diabetes (Figure 7) and increased vascular risk (-> myocardial infarct, cerebral ischemia, infarcts in all the vascular districts, heart hypertrophy and failure, etc.) [9]
Occupational noise, smoking, high Body Mass Index -> hearing loss [36]
Excessive exposure to noise -> hearing loss [9,37]
Smoking and/or air pollution -> chronic bronchitis [38], emphysema [39]
Smoking -> coronary heart and other cardiovascular diseases, chronic respiratory diseases, pregnancy complications, and respiratory diseases in children [40], lung [40,41] / larynx [41,42] / bladder [41,43] / kidney [35] / pancreas [44] carcinoma, peptic ulcer [45,46]
Excessive ingestion of simple and refined carbohydrates (in particular sugar) and other dietary modifications -> dental caries, pyorrhoea, crowded teeth [9,25] (Figure 8)
Scarce ingestion of fibre -> constipation, colon diverticulosis, colon carcinoma, stomach carcinoma, type 2-diabetes, metabolic syndrome and cardiovascular diseases [47], appendicitis [48,49]
Scarce ingestion of calcium and reduced physical activity -> osteoporosis [9,50], back pain [9]
Reduced exposure to natural allergens in the childhood -> allergies [51]
Exposure to chemical substances artificially synthesised -> allergic diseases [52]
Altered conditions of sociality, stress of civilised condition -> mental and psychiatric disorders [3,9]
Various factors -> increased incidence of various types of cancer [9,53]
Alcoholism -> hepatic steatosis, steatohepatitis, cirrhosis [54], larynx carcinoma [42]

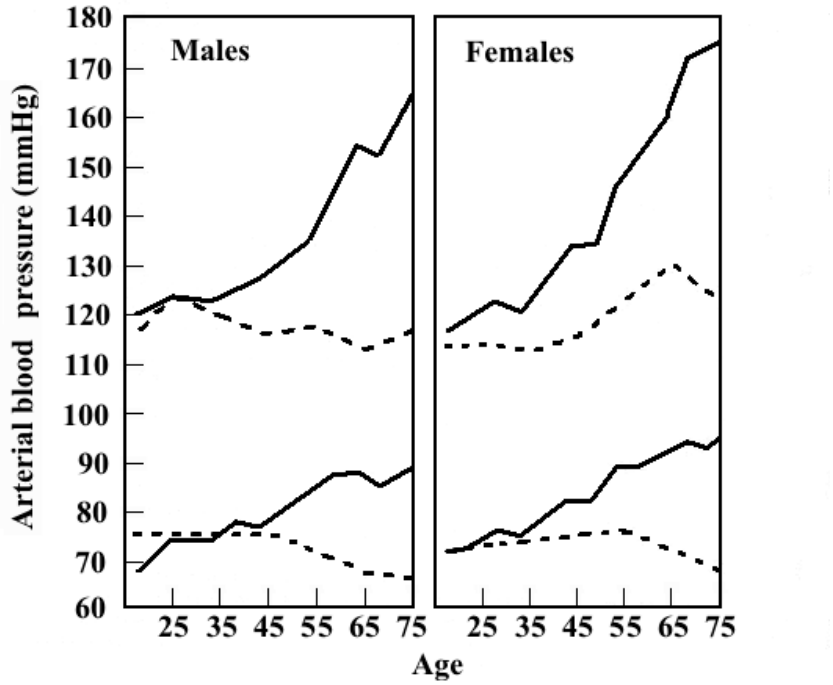
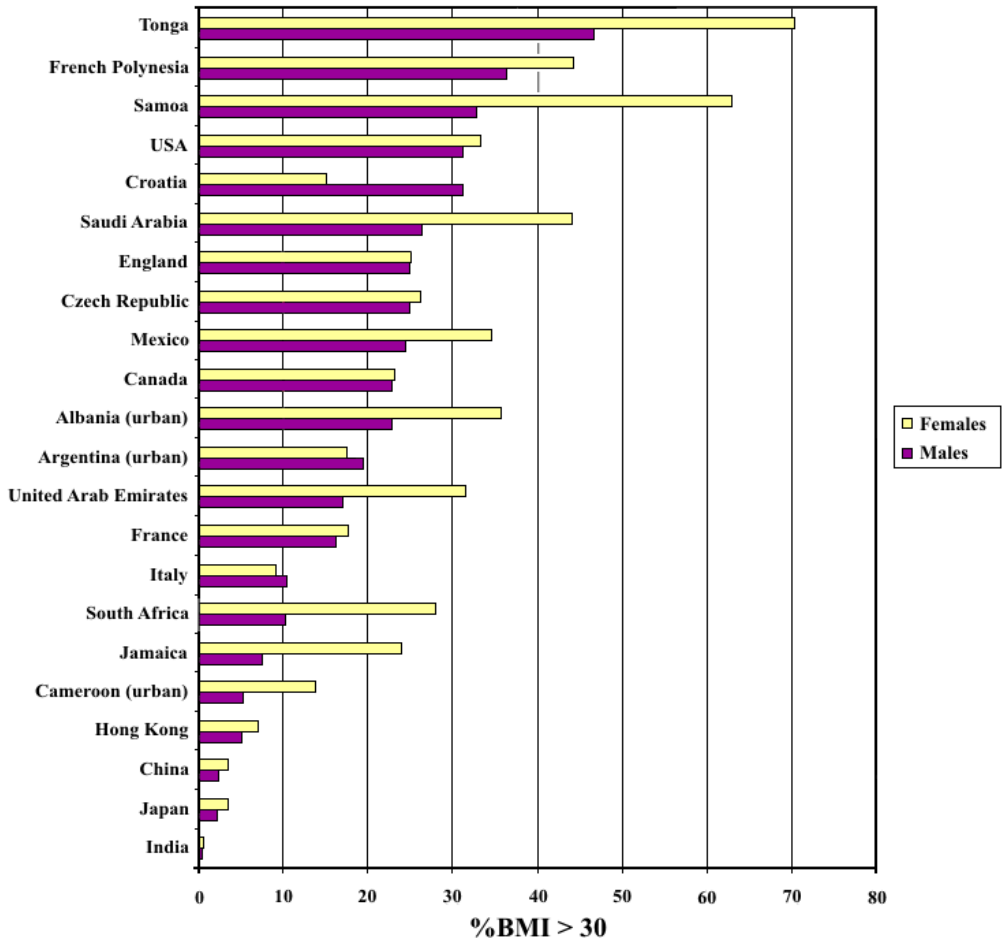


Figure 5. Arterial blood pressures in !Kung individuals (dashed lines) and in London citizens (continuous lines) [55] (partially redrawn).



Data from International Obesity Task Force (from late 1990s to 2002; http://www.iotf.org/database/documents/GlobalPrevalenceofAdultObesityJuly08pdfv2.pdf).

Figure 6. Frequencies of Body Mass Index > 30 in some countries. Some years ago, for the few remaining hunter-gatherer populations, obesity was a rarity [26].

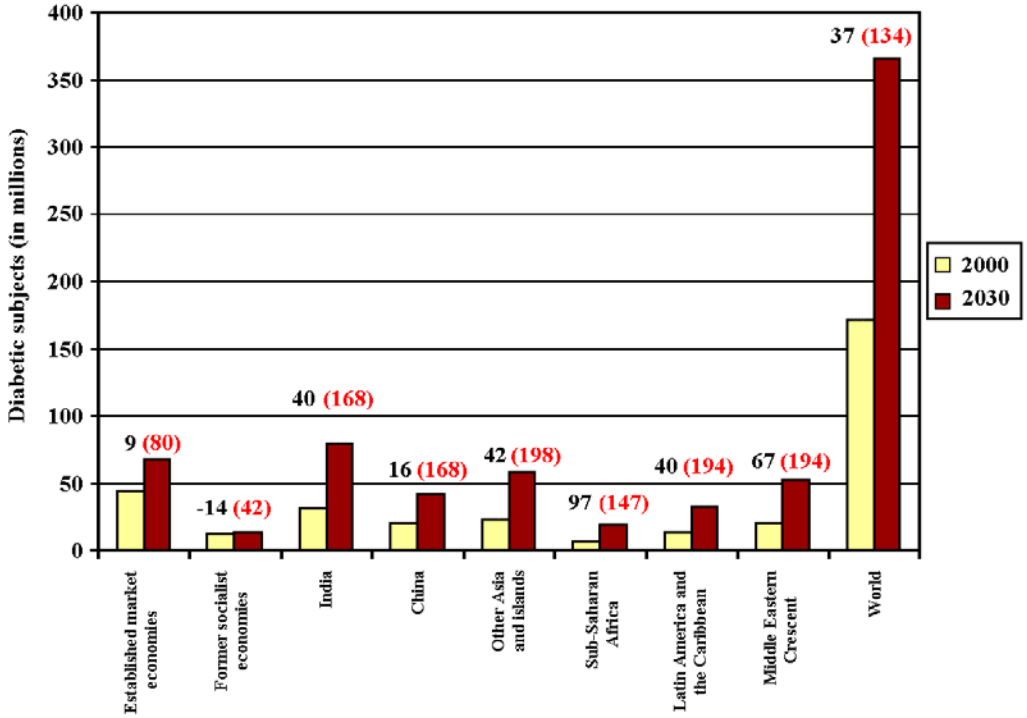


Figure 7. Estimated numbers (in millions) of people with diabetes by region for 2000 and 2030. Percentage of change in total population and (between brackets) percentage of change in population >65 years of age are also indicated [56]. Diabetes was a rarity in the few remaining hunter-gatherer populations [26].

Figure 8. In the upper side: photos of indigenous and of skulls from people following ancestral dietary habits ("teeth ... excellent and free from dental caries"); in the lower side: photos of indigenous following modern diets (multiple dental caries, "crowding of the teeth", "changes in facial form", pyorrhoea) [25]. After about 70 years from publication, the evidence and the teaching of the extraordinary book of Price (called the "Charles Darwin of nutrition") is still perfectly topical and could be a symbol of the damages caused by thoughtless changes of the ecological niche.

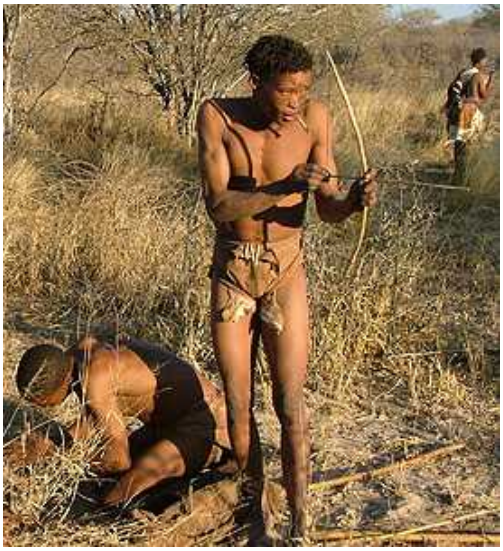
It is essential a distinction between “proximate” and “evolutionary” causes of a disease [3]. Evolutionary (or ultimate or primary) causes explain “why” diseases happen. Proximate (or near) causes explain “how” diseases manifest themselves.

Genes making an individual vulnerable to a disease in particular conditions are the “proximate” causes, while the “evolutionary” cause is that an individual is exposed to ecological conditions to which the species is not adapted. For example, a “normal” modern diet includes an intake of salt more than ten times that estimated to be ingested in prehistoric times or in modern hunter-gatherer societies. Our body is not adapted to this “normal” intake of salt and, after years of excessive use of salt, “hypertension-predisposing” genes cause hypertension. The true cause of hypertension is the abnormal excessive intake of salt to which the organism is not adapted (evolutionary cause) and not the existence of “hypertension-predisposing” genes (proximate cause). The “normality” of modern diet is correct in its statistical meaning (average intake of salt in a modern population) as it is correct to say that blindness is statistically “normal” in a community of blind men. It should be stressed that “normal” modern diet is largely abnormal in evolutionary terms and that “hypertension-predisposing” genes are normal genes that in the modern harmful conditions of life cause hypertension. The pathological condition is the modern “normal” diet and not “hypertension-predisposing” genes and the attention should be focused on the real causes and their possible correction and not on proximate causes (Figure 9).

(A) **(B)**

Figure 9. A) The victims of the Holocaust numbered in the millions (Hebrews, Roms, gays, political dissidents, etc.). Misleading interpretation (proximate cause): this was caused by their race, religious creed, etc. Correct interpretation (primary cause): this was caused by an insane and murderous ideology. B) The victims of diabetes, hypertension, atherosclerosis and their complications number in the tens of millions. Misleading interpretation (proximate cause): this is caused by their diabetes-, hypertension-, atherosclerosis-predisposing genes. Correct interpretation (primary cause): this is caused by alterations of the ecological niche (too many calories and unsaturated fats, too much salt, etc.) to which the organism is not adapted.

The mismatch between the ecological niche to which our genes are well adapted and the actual habits is the true (“primary”) cause of large part of our ills (“Discordance Hypothesis”) [9] (Figure 10).



(A)

(B)

Figure 10. A) Bushmen tribes (!Kung San, Botswana), some years ago one of the few remaining hunter-gatherer populations, had a lifestyle analogous to Stone Age societies. They were quite well adapted to their ancient ecological niche and diseases such as hypertension, diabetes, obesity, cardiovascular affections, cancer, psychological and emotional ailments, dental caries, myopia, astigmatism, etc., were rare events for them;
B) Modern men. Their genes are practically the same of hunter-gatherer men but there is a noxious "discordance" between their habits and the ecological niche to which their genes are adapted: the above-mentioned affections, and many others, are the terrible consequence [9].

3. Diseases Caused by Interactions with Other Species

As there is continuous competition among the species with conflictual evolutionary exigencies and, in particular, between an organism and its parasites (bacteria, viruses, fungi, protozoa, parasitic worms, etc.), a third general cause of disease is predictable.

The number of bacteria living in the gut of each man has been estimated to be ten times the number of his cells [57] and there are trillions of other bacteria living on our skin, mucosae and elsewhere on or in our body. Large part of these bacteria live with us without being harmful and often are useful, e.g., hindering settlement and attack of bacterial pathogenic species.

"The total set of over 1400 pathogen species breaks down into over 200 viruses, over 500 bacteria and rickettsia, over 300 fungi, over 50 protozoa, almost 300 helminths, and at least 2 kinds of prion" [58].

In this category of diseases, natural selection acts both on the side of the host and on the side of its parasites. The result must be a compromise between the competing exigencies to survive and propagate of both host and parasites.

The relationship between an organism and its parasites is analogous to that between a prey and its predators, and in it we have a troublesome position analogous to that of a prey. However, it is predictable that, in a similar way to what happens in the prey-predators case [59], to minimise disadvantages and maximise advantages both for host and parasite, parasites will damage more very young, sick and old individuals, with low reproductive potentiality, and less intermediate ages and healthy individuals with greater reproductive potentiality.

4. Diseases Caused by Conditions beyond Adaptation Range

Conditions beyond the adaptation range of the species (e.g., the fall of a man from an excessive height, the trauma of a violent car accident, etc.) are a sure cause of physiological dysfunctions or death.

5. Disease-Like Phenomena Caused by Natural Selection

Natural selection may determine disease-like phenomena, which may be apparently harmful or which are surely harmful in terms of individual fitness.

For this category of phenomena, which cannot be defined as diseases, a subdivision is necessary on the grounds of the selective mechanisms involved.

5.1. Phenomena That Are Defences against Harmful Agents

Natural selection favours physiological mechanisms that are defensive against infections and other harmful agents or conditions (e.g., fever, cough, sneezes, itch, inflammatory phenomena, nociceptive pain, diarrhoea, iron deficiency, morning sickness, emotions such as anxiety, fear, etc.) [2].

In particular: 1) iron deficiency, especially in pregnancy, appears an effective defence against infectious diseases [3,60] because: “Acquiring iron is a fundamental step in the development of a pathogen, and the complexity and redundancy of both host and pathogen mechanisms to acquire iron and control flux and availability illustrate the longstanding and ongoing battle for iron.” [61]; 2) morning sickness of the pregnant woman protects the embryo from foods containing teratogen chemicals (e.g., natural toxic chemicals in vegetables) or potentially infected (e.g., meats, fish, poultry, and eggs) [62,63].

In certain cases, which must be considered as pathological noxious conditions of alteration of physiological and beneficial functions, the defensive mechanism is excessive or inappropriate or harmfully altered by a parasite to increase its propagation (e.g., diarrhoea in infections by *Vibrio cholerae* [64]).

5.2. Phenomena Damaging Other Individuals Genetically Related but Improving Overall Fitness of Progeny

Vertebrate immune system must discriminate between antigens of each host individual and those of the parasites, which try to overcome immunologic defences by using for their coverings proteins with the same antigenicity of the host (antigen mimicry). The defence of

the host against antigen mimicry is to have the greatest inter-individual variability of antigen formulas so that a mimicry adapt to infect all the potential hosts is impossible [10]. The major histocompatibility complex (MHC) is the main tool by which the host organism obtains an extraordinary antigen variability. Differences between antigenic formulas of host and parasite give greater resistance to the infection while similarities cause susceptibility. Correlations between resistance or susceptibility to several infectious or infection-related diseases and specific human MHC alleles are well documented [65,66].

The best progeny is that with the greater antigen variability. This may be obtained through MHC-mediated mate choice and with post-copulatory selection. The first phenomenon has been observed in several vertebrate taxa and is widespread in nature [67]. MHC genes influence human mating preferences. Women college students rated the odours of MHC-dissimilar men as being 'more pleasant' than those of MHC-similar men [68,69]. In an isolate, ethnically homogenous community, significantly fewer couples was observed to match at a 16-locus MHC haplotype [70,71].

With the second phenomenon, also referred to as 'cryptic female choice' [72], miscarriage eliminates the production of offspring with lesser antigen variability having a future decreased fitness due to diminished disease potential resistance [73]. For animals, post-copulatory selection is well documented [74]. For humans, in a study, an excess of MHC-heterozygotes was found in newborn males [75]. A series of studies on an isolate and ethnically homogenous community have documented that couples with shared HLA-DR alleles in comparison with couples not sharing the same alleles have significantly less children [76], a greater interval between pregnancies [77] and a greater pregnancy loss rate [78].

In this sub-category, natural selection determines the death of healthy embryo individuals to optimise the survival potentiality of progeny. Infanticide or the abandonment of healthy new-born babies when the resources are insufficient are ancient and widespread behaviours [79], apparently determined by analogous evolutionary necessities of not giving place to progeny with reduced survival possibilities and that could subtract precious resources to kin individuals [9]. For animals, analogous behaviours are well known [59]. This sub-category indicates that natural selection may cause physiological events that could be interpreted as pathological or behaviours considered ethically unacceptable in our culture. This implicates that from an ethical point of view not all the effects of natural selection can be accepted uncritically or regarded in principle as not to be modified.

5.3. Phenomena Damaging the Individual but Favoured by Kin Selection

In the classic definition of natural selection, the variation of the frequency of a gene X between two generations (Δ_x) is depending on the advantage or disadvantage s caused by X, alias the variation of fitness, and of the reproductive value P of the individual in which X acts:

$$\Delta_x \propto s \cdot P \tag{8}$$

The definitions of inclusive fitness and kin selection have strongly modified this concept [59,80,81,82,83]. If a gene X, present in the individual I_1, determines effects on I_1 and on

other individuals I_2, I_3, ... I_n genetically related (kins) to I_1, with coefficients of relationship (probability of genes in common) equal to r_2, r_3, ... r_n, respectively, and with reproductive values equals to P_1, P_2, P_3, ... P_n, respectively, to evaluate the spreading or decay of X within the species, the effects on the fitnesses of all individuals involved must be considered:

$$\Delta_x \, Q \, \Sigma \, (s_z \cdot P_z \cdot r_z) \qquad (9)$$

with z varying from 1 to n.

Only if no other individual than I_1 is involved in the action of X, formula (9) is transformed in the classic formula (8), as $r_1 = 1$.

This conceptual revolution allowed a convincing explanation of the social organisation of ants and bees and of many other otherwise inexplicable phenomena [59].

Inclusive fitness and kin selection are indispensable to understand the phenomena illustrated in this sub-category.

5.3.1. Altruistic Actions

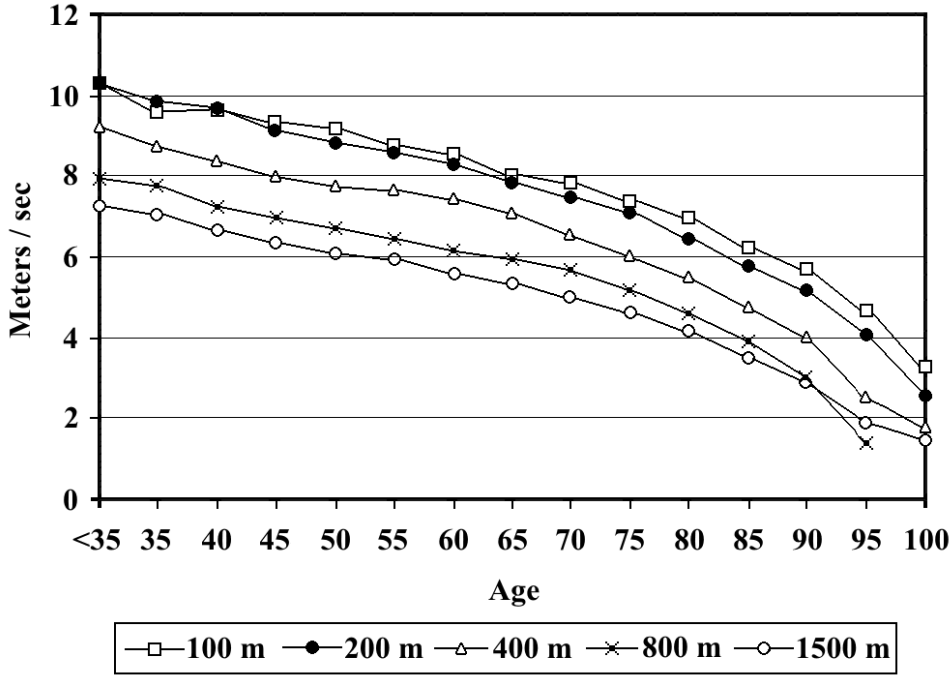
For animals, behaviours or actions that damage or kill the individuals expressing them but increase the survival probabilities of kin individuals are well documented [59], e.g., the defence from predators of a drove of yellow baboons (*Papio cynocephalus*) [84] or of chacma baboons (*Papio ursinus*) [85] by the predominant males with great individual risk.

Actions damaging an individual and favouring kin individuals do not necessitate a wilful choice or even the existence of a nervous system. For example, apoptosis is a form of cell death genetically determined and highly regulated, for the first time described as phenomenon other than necrosis in normal liver epatocytes [86] and typical of eukaryotic organisms, even if monocellular [87]. In the yeast (*Saccharomyces cerevisiae*), the scarcity of nutrients triggers the apoptosis of older individuals enhancing “the chances of the rest of the population to survive and to sporulate, thus increasing the probability that the clone will survive” [88] and this is explained as “altruistic cell death” [88]**,** alias as an “altruistic behaviour” [89] caused by kin selection.

For humans, behaviours and actions that reduce fitness or jeopardise health, and even life of individuals committing them, are well known and can be interpreted as altruistic behaviours determined by kin selection [90,91].

5.3.2. Ageing

For many species, ours included, an age-related fitness decline is well documented both in wild and in protected conditions [92,93,94,95,96,97,98,99,100]. This fitness decline is illustrated by the age-related continuous decline of athletic performances (Figure 11), which is mirrored in the age-related mortality increase: “No one would consider a man in his thirties senile, yet, according to athletic records and life tables, senescence is rampant during this decade” [101].



Source of data: for age group < 35 (world records), http://en.wikipedia.org/wiki/World_records_in_athletics; for other age groups, http://www.world-masters-athletics.org/records_output/rec_list_outdoor_m.php.
Figure 11. Age-related fitness decline.

In its more advanced manifestations, this phenomenon is universally known as ageing / senescence, but the use of these terms is scientifically tricky being often referred only to the more evident expressions of the fitness decline, rarely observable in the wild ("...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" [11]). To avoid misunderstandings, other terms precisely describing the phenomenon as "increasing mortality with increasing chronological age in the wild" (IMICAW) [13] or "actuarial senescence in the wild" [99,100] or "age-related fitness decline in the wild", which do not refer to lower limits for the grade of fitness decline, are preferable.

A widespread opinion is that the age-related fitness decline in the wild is the result of insufficient selection at older ages against harmful mutations accumulated over evolutionary time (mutation accumulation theory) [102,103,104,105,106].

Against this hypothesis, it has been demonstrated that even with a great number of noxious gene expressing their harmful action at ages with a few survivors, natural selection reduces greatly frequencies and effects of the noxious genes so that life table is scarcely modified by their action (Figure 12). The conclusion, till now not falsified, is that mutation accumulation theory is untenable as explanation of age-related fitness decline in the wild [10,13,21].

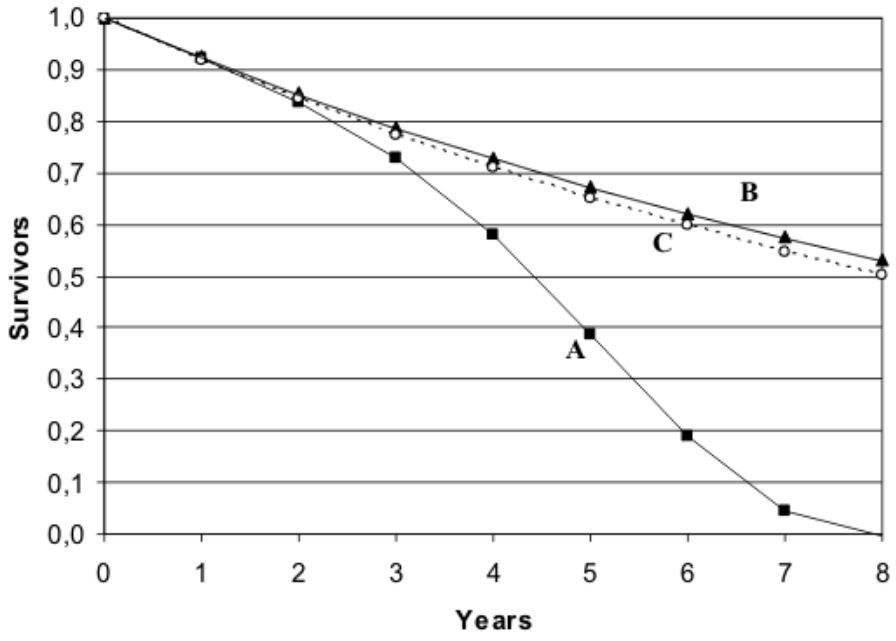


Figure 12. Curve A is the life table in the wild of a real species showing an age-related fitness decline. Curve B is a hypothetical life table of the same species with only the extrinsic mortality at its lowest value and without the age-related fitness decline. Curve C is a hypothetical life table with the same mortality of curve B plus the effects of a great number (n = 500 / year) of noxious genes acting at years t_1, t_2, ... Curve A is quite different from curve C and, therefore, it is unjustifiable as an effect of noxious genes insufficiently eliminated by natural selection [21].

To overcome the weakness of mutation accumulation theory, two new hypotheses were proposed. The first (antagonistic pleiotropy theory) suggested that fitness decline was determined by pleiotropic genes, beneficial at early ages and harmful at later ages [101,107]. The second (disposable soma theory) proposed that the causes of fitness decline were environmental or somatic and that at older ages natural selection was limited by physiological or environmental constraints, so that, in the subdivision of metabolic resources between reproduction and maintenance, reproduction was preferred [108,109].

However, “Few plausible candidates for antagonistically pleiotropic genes have been recognized, and the physiological mechanisms connecting opposing early and late effects on fitness are not well characterized ...” [100] and there is no proof of trade-off between greater reproduction and lesser longevity for primate and humans [110]. In an authoritative paper [11], no example of trade-off is reported for animals that show age-related fitness decline in the wild (documentation of trade-offs for animals that show age-related fitness decline in artificial conditions is reported, but this is a different phenomenon not subjected to natural selection [21,22]).

The common view of these three theories is that they consider age-related fitness decline as a nonadaptive phenomenon. Current gerontological theories reply to “Darwin’s dilemma” [16,18] (Is ageing nonadaptive and therefore a great example of failure of natural selection or

adaptive by being somehow evolutionarily advantageous?) maintaining that natural selection fails to make individuals very long-lived or not showing age-related fitness decline.

In clear contrast with this idea, age-related fitness decline has been explained as evolutionary advantageous in terms of kin selection in particular ecological conditions [10,13,21]. Afterwards, in accordance with the theoretical arguments but independently of them, empirical data in support of an adaptive meaning of fitness decline and against hypotheses interpreting age-related fitness decline as nonadaptive have been presented [22].

Indeed, only the heretical idea that age-related fitness decline is adaptive, hinted by various authors [13,14,15,20,21], allows to justify:

1) *the existence of species with no age-related fitness decline in the wild.* The individuals of many species survive in the wild till remarkable ages showing no detectable fitness decline (e.g., sturgeon, rockfish, turtles, bivalve mollusks, certain perennial trees, etc.; "animals with negligible senescence" [98]). For this phenomenon, truly strange for nonadaptive theories [111], particular variants of disposable soma theory have been developed [108,109], even to justify the case in which mortality rate decreases at greater ages [112]. However, these variants have the taste of adaptations *ad hoc* to justify data contrasting with theoretical predictions.
2) *the inverse relation of extrinsic and intrinsic mortality documented for some bird and mammal species in the wild* [100]. Current nonadaptive theories predict explicitly a direct relation and Ricklefs states clearly in his discussion that this prediction is confuted by empirical data [100]. On the contrary, adaptive theory predicts the inverse relation observed [10,13,21,22].
3) *the existence of sophisticated mechanisms, genetically determined and regulated, progressively limiting cell turnover and cell functionality.* The telomere-telomerase system limits cell duplication capacities (replicative senescence) and, consequently, cell turnover and, moreover, causes a progressive decay of cell functionality (cell senescence) [113]. These mechanisms, genetically modulated and determined, which are a plausible cause of the progressive fitness decline [21,113], are not explained by nonadaptive hypothesis while are necessary for the validity of the adaptive hypothesis [22]. In particular, nonadaptive hypothesis tries to explain replicative senescence and cell senescence as a defence against malignant neoplasia [114,115], that is a terrible evolutionary trade-off between ageing and defence against cancer [116], but: a) old individuals of "animals with negligible senescence" such as rainbow trout and lobster show in the wild the same telomerase activity of young individuals [117,118] and no increase in cancer vulnerability, as their stable mortality rates prove; b) replicative senescence and cell senescence weaken the efficiency of immune system [113], a factor inversely related to cancer vulnerability and incidence [119]; c) shortened telomeres increases cancer probabilities because of dysfunctional telomere-induced instability [120,121]. Moreover, replicative senescence and cell senescence, although not caused by telomere shortening but by another unknown mechanism related to the number of duplications, are well documented in eukaryotic species such as yeast [122,123,124], which being unicellular species cannot be affected by cancer. However, these phenomena and others strictly associated

[125,126] observed in yeast have been interpreted as adaptive [20,127,128,129,130,131] and they are consistent with the explanation that they determine a greater evolution rate and are favoured in conditions of K-selection [13].

Telomere-Telomerase System

It is known for many years that, in general, normal cells have a limited capacity of duplication (Hayflick limit) *in vitro* [132,133] and *in vivo* [134], documented for many types of cells [135,136,137], related to the life span of the species from which cells are derived [138], inversely related to the ages of donors of origin [139] and caused by something acting in the nucleus [140].

The cause of the Hayflick limit was hypothesised to be the progressive shortening of the DNA molecule at each duplication [141], as DNA polymerase cannot replicate a whole molecule of DNA and a little terminal portion of DNA would be ignored in replication [142].

One of the ends of DNA molecule (telomere) is constituted by a repetitive sequence, shown to be TTGGGG in a protozoan [143], and later for mammals, man included, to be only a little different (TTAGGG) [144] but common to many other species [145]. As hypothesised, telomere was proved to shorten at each duplication [146].

An enzyme, telomerase, capable to elongate telomere at each duplication, annulling DNA polymerase insufficiency, explained the existence of cells with unlimited duplication capacities, such as germ line cells [147]. It was shown that telomerase is present in immortal human cell lines [148] and repressed by regulatory proteins [149]. Its deactivation causes telomere shortening at each replication and the reduction of duplication capacity [150], while with its activation telomeres resulted elongated and cells acquired unlimited duplication capacities [151,152,153,154,155].

The final blockage of cell duplications (replicative senescence) is not an abrupt phenomenon but a progressive increase in the probability of blockage depending on telomere residual length [156,157]. Telomere is capped by particular protective nucleoproteins and oscillates between capped and uncapped states, with the duration of the capped state in direct relation to telomere length and with vulnerability for the passage to “noncycling state” (replicative senescence) in the uncapped state [158].

As stem cells, unlike germ cells, have levels of telomerase activity capable to restore only partially telomere length [159], *in vivo* stem cells even with partially shortened telomere, that is with a slight probability to pass to replicative senescence, could not duplicate unlimitedly [113].

The modulation of the telomere-telomerase function is likely different for each species [113] and this could explain why species with long telomeres [160] age precociously.

In correlation with telomere shortening, the overall cell functionality declines (cell senescence). This decay, as replicative senescence, is surely in correlation with the relative shortening of telomere (Fossel’s “cell senescence limited model”) [113]. In particular, experiments provoking telomerase activation reverse both replicative senescence and cell senescence [151,152,155]. The mechanism of cell senescence is likely a progressive repression of a subtelomeric DNA portion (transcriptional silencing), which regulates the

overall cell functionality, caused by the progressive sliding of the protective nucleoproteins ("heterochromatin 'hood' ") of probable fixed length capping telomere and adjacent DNA in correlation with telomere shortening [113] (Figure 13).

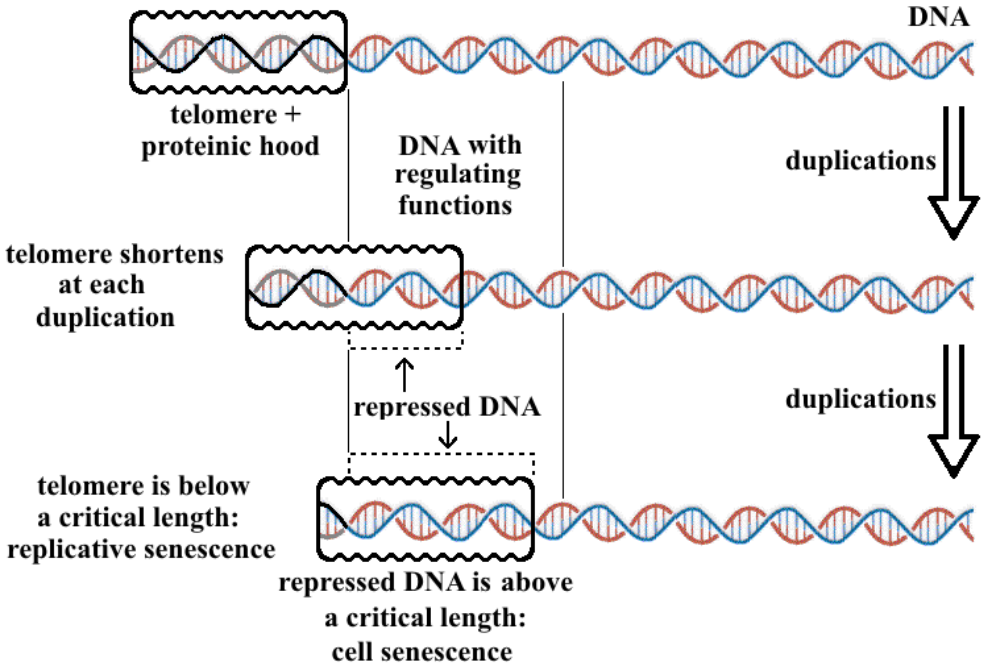


Figure 13. Telomere progressive shortening impairs the expression of many genes. It is likely the existence near to the telomere of a tract of DNA regulating overall cell functionality: with telomere shortening the proteinic "hood" capping the telomere slides down and alters this regulation.

The placing of a portion of DNA with essential regulatory activities in a position progressively impaired by telomere shortening is a strong element in support of the hypothesis that telomere-telomerase limits are adaptive.

In short, the limitation of cell duplication capacities and its modulation appear clearly to be not caused by insuperable physiological constraints but determined and regulated by genes specifically favoured by natural selection as adaptive.

Cell Turnover

Our body is composed of cells in continuous turnover with rates different for each cell type. It has been estimated that each year a mass of cell equal to our entire body weight is lost and substituted [161]. Even for some types of cells considered perennial, there is now evidence that they are subject to turnover (heart myocytes [162], muscle myocytes [163,164,165]). For other types of cells surely perennial, there is dependence on other cells with turnover, such as for the neurons on the gliocytes [113].

In normal conditions, cell elimination is the result of various forms of "programmed cell death" (PCD), such as removal by macrophages (red cells), keratinization and detaching from the somatic surface (skin) and apoptosis. In particular, apoptosis, an ordinate process of self-destruction with non-damaging disposal of cellular debris, was described for the first time as a phenomenon different from necrosis in a normal liver [86], is related to cell turnover in healthy adult organs [166,167,168] and is documented for many healthy tissues and organs [156,169,170,171,172,173,174,175,176,177,178,179,180].

The continuous elimination of cells by PCD must be balanced with the replication of appropriate stem cells and this cell turnover is limited by the genetic regulation of the telomere-telomerase system.

In short, for vertebrates but not for all animals (e.g., the adult stage of *Caenhorabditis elegans* has a fixed number of cells), three categories of cells are currently distinguished:

1) Those with high turnover: e.g., intestinal crypts cells [181];
2) Those with moderate turnover: e.g., cells of the deep layers of skin and endothelial cells [182], heart myocytes [162], muscle myocytes [163,164,165].
3) Those with no turnover, e.g., neurons, with a few possible exceptions [183] but always metabolically depending on gliocytes that are cells with turnover [113].

Atrophic Syndrome

The progressive shortening of telomeres, if we accept Fossel's cell senescence limited model [113], causes an "atrophic syndrome" characterised by:

a) increasing number of cells in replicative senescence (overall reduction of cell duplication capacities);
b) slowdown of the cell turnover;
c) reduction of the overall number of cells (atrophy);
d) hypertrophy of the remaining specific cells;
e) possible substitution of the missing cells with nonspecific cells;
f) increasing number of cell with altered functions (cell senescence);
g) dysfunctional telomere-induced instability with consequent vulnerability to cancer [120].

A General Scheme for Ageing

It is easy to infer that cell turnover limitations caused by the telomere-telomerase system and linked or derived phenomena (cell senescence, atrophic syndrome, etc.) cause all the morphological and functional alterations that determine the fitness decline and, in their more advanced expression, the senile state (Fossel's cell senescence general model of ageing [21,113]) (Figure 14).

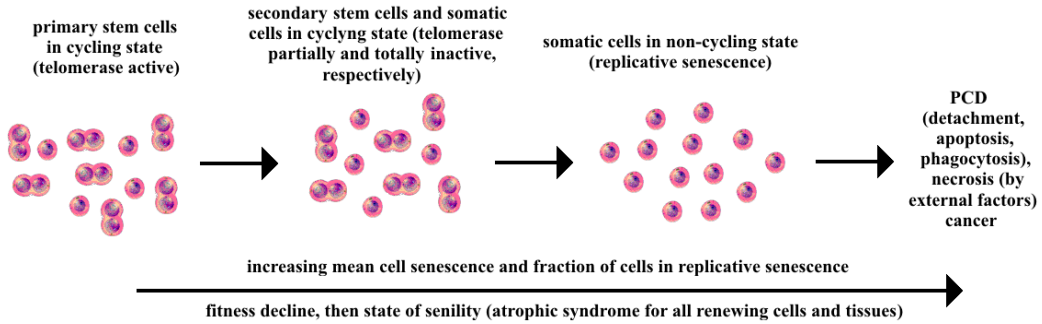


Figure 14. From primary stem cells with active telomerase, secondary stem cells and somatic cells with replicative capacity originate, but with telomerase partially and totally inactivated, respectively. From both types of cells, somatic cells in replicative senescence originate. Replicative senescence and cell senescence contribute to fitness decline that gradually becomes the senile state.

In support of this hypothesis:

1) for mice, a factor inducing apoptosis and cell cycle arrest, provokes osteoporosis, a diminished stress tolerance, atrophy of all organs and a reduced longevity [184];
2) in a rare human genetic disease (dyskeratosis congenita [185]), in which telomerase activity is low and telomeres are shorter than normal [186], tissues in which cells multiply rapidly (skin, nails, hair, gut and bone marrow, etc.) manifest precociously severe dysfunctions (alopecia, nail dystrophy, gut disorders, failure to produce blood cells, etc.) [182]. In this syndrome there is also a high cancer rate due to telomerase deficiency that cause unstable chromosomes [155,187].
3) in another genetic disease, Werner syndrome, in which cell replication is impaired [188,189] and there is a limited replication capacity [139], tissues composed of cell with moderate turnover suffer from severe alterations (e.g., alterations in lens epithelial cells, endothelial cells, Langherans β-cells, various types of derma cells provoke cataracts, atherosclerosis, type 2-diabetes, regional atrophy of subcutaneous tissue and skin atrophy, respectively) [190].

Examples of Normally Ageing Tissues

Intestinal Villi

In each intestinal crypt, there are four to six stem cells that with their intensive duplication activity renew continuously the epithelium of the small intestine [191]. In healthy old individuals, in comparison with young individuals the transit time for cells from crypts to villous tips increases and villi become broader, shorter and with less cellularity [192] (Figure 15). These changes, surely due to a declining mitotic activity of crypt stem cells, as hypothesised from a long time [192], reduce intestinal functionality and, likely, overall fitness.

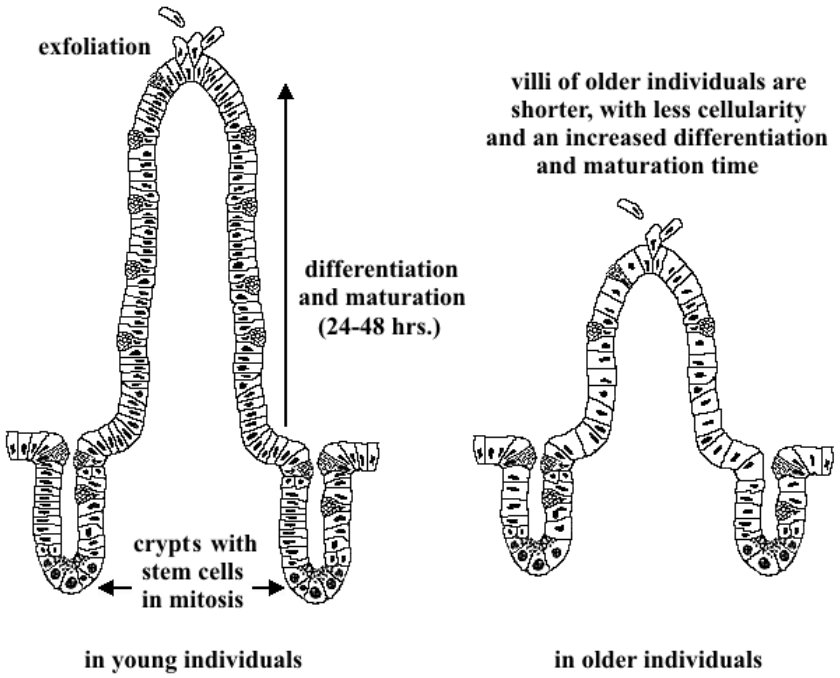


Figure 15. Intestinal villi in young and older individuals.

Endothelium

Endothelial cells manifest a continuous turnover assured by endothelial progenitor cells, derived by primary stem cells of bone marrow, and numerically in inverse relation with age [193]. A slackened turnover of endothelial cells increases the probability of endothelial dysfunction and, therefore, of diseases derived from altered blood circulation such as myocardial infarction and cerebral ischemia: indeed, the number of endothelial progenitor cells is a predictor of cardiovascular risk equal to or more significant than Framinghan risk score [193,194]. Diseases derived from compromised blood circulation are a common end to the life of healthy old individuals with no particular risk factor [195].

Epidermis

Human epidermis turnover is determined by stem cells located in the dermal-epidermal junction, a corrugated surface. In old subjects, dermal-epidermal junction is flattened, an indirect sign of the reduction of epidermis stem cells, and the rate of epidermal renewal is reduced [196]. In derma, as a likely consequence of the exhaustion of specific stem cells, a

general reduction of all its components (melanocytes, Langerhans cells, dermal fibroblasts, capillaries, blood vessels within the reticular dermis, mast cells, eccrine glands, hair. etc.) is reported and nails grow more slowly [196].

Photoreceptor Cells

Photoreceptor cells (cones and rods) are highly differentiated nervous cells with no turnover, but metabolically depending from other cells with turnover, retina pigmented cells, which are highly differentiated gliocytes. Each day, with an extraordinary metabolic activity, every retina pigmented cell phagocytizes about 10% of the membranes with photopsin molecules of about 50 photoreceptor cells. With the age-related decline of retina pigmented cell turnover, the deficiency of their function kills the photoreceptors not served. This is above all manifested in the functionality of the more sensitive part of the retina, the macula, from which the name “age-related retina macular degeneration” (AMD) [197]. AMD affects 5%, 10% and 20% of subjects 60, 70 and 80 years old, respectively [198], and it is likely that a large proportion of older individuals suffer from AMD.

Neurons

Neurons are perennial cells but their vitality depends on other cells (e.g., microglia, a type of gliocytes) that show turnover. The hypothesis that Alzheimer Disease (AD) is caused by replicative senescence and cell senescence of microglia cells has been proposed [113,199].

Microglia cells degrade β-amyloid protein [200,201] and this function is known to be altered in AD [202] with the consequent noxious accumulation of the protein.

Telomeres have been shown to be significantly shorter in patients with probable AD than in apparently healthy control subjects [203]. AD could have, at least partially, a vascular aetiology due to age-related endothelial dysfunction [113] but “A cell senescence model might explain Alzheimer dementia without primary vascular involvement.” [113]

An interesting comparison between AD and AMD is possible: both are probably determined by the death of cells with no turnover as a likely consequence of the age-related failure of cells with turnover (Figure 16). Moreover, AD frequency, as AMD, affects 1,5% of USA and Europe population at age 65 years and 30% at 80 [204] and a centenarian has a high probability of suffering from it.

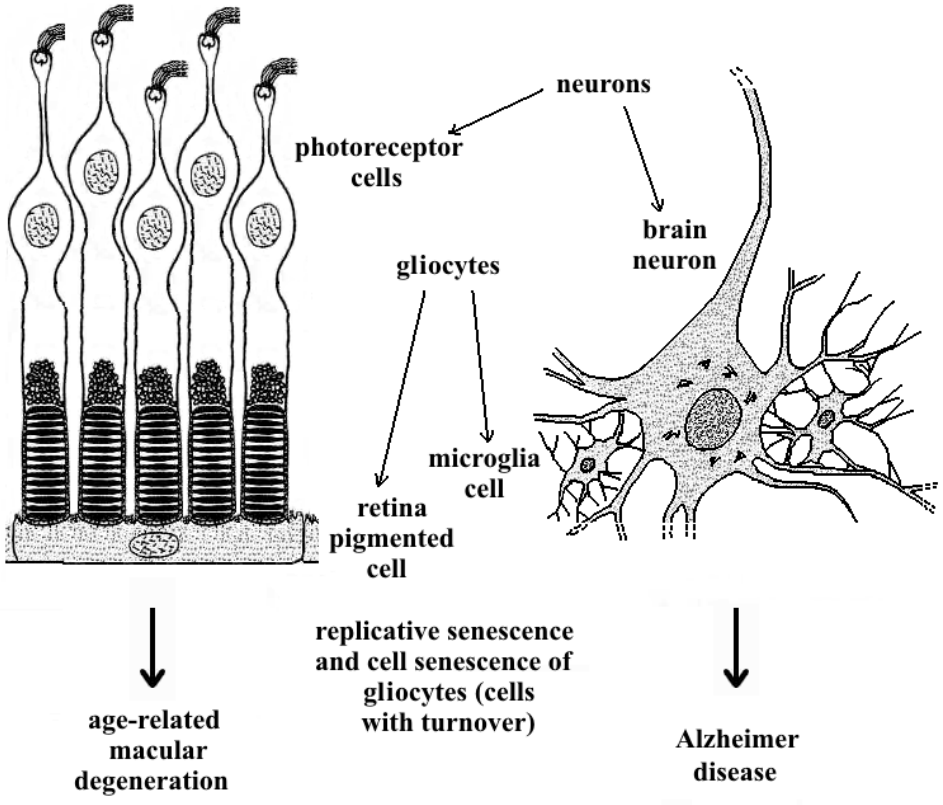


Figure 16. Schemes of retina photoreceptors and of a brain neuron (both neurons) served by two types of differentiated gliocytes, retina pigmented cells and microglia cells, respectively. Replicative senescence and cell senescence of retina pigmented cells and of microglia cells cause age-related macular degeneration and Alzheimer disease, respectively.

Other Organs/Tissues

In relation to the progressive failure of cell turnover, senescence in healthy subjects is also characterised by age-related: bone loss (-> osteoporosis), muscle atrophy (-> sarcopenia), reduction in the number and in the size of nephrons with consequent decline of renal function (-> renal insufficiency), atrophy of pulmonary alveoli (-> latent / manifest emphysema), decline of liver volume with increased size of the remaining epatocytes (-> latent / manifest hepatic insufficiency), loss of myocytes with hypertrophy of the remaining myocytes and enlargement of cardiac cavities (-> cardiac failure), reduction in the number of pacemaker cells in the sinus node (-> atrioventricular block and other arrhythmias), decline in the number and activity of pancreatic β-cells (-> latent / manifest diabetes mellitus), atrophy of gastric mucosa (-> atrophic gastritis), declining activity of lens epithelial cells (-> nuclear cataracts), atrophy of large intestine, atrophy of salivary glands, decrease of taste buds, thinning of the lingual epithelial, involution of red marrow with increasing decline of the number and activity of cells with hematological and immunological functions, etc. [195].

Moreover, telomere dysfunction in cells in replicative senescence, in particular those, mostly epithelial, with higher turnover, is a significant cause of cancer in older individuals [120].

Finally, we must consider the numberless complications for many organs deriving by the progressive impairment of endothelial, neuronal and immunological functions and, in general, by the interlacement of the decline of several functions [195].

Ageing in Short

The empirical evidence shows that an ageing individual suffers from a generalised atrophic syndrome and that death will be caused by the critical failure of one or several impaired functions. The atrophy of each tissue or organ is explained by the decline in cell turnover (Fossel's cell senescence general model of ageing [21,113]), which is caused by the limits of the telomere-telomerase system (Fossel's "cell senescence limited model" [113]).

The ageing phenomenon is therefore caused by limits genetically determined and regulated in a complex system [21] and these limits can be evolutionarily justified only accepting an adaptive meaning for fitness decline [16,18,21,22].

This conception is radically different from that currently accepted, which maintains:

1) *Ageing does not describe a distinct entity and is only an useful term to describe the numberless afflictions of the old age*. In fact, in the International Classification of Diseases (ICD-9-CM, http://icd9cm.chrisendres.com/), which has code numbers for each disease or physiological event needing medical advice (e.g., pregnancy, delivery, etc.), there is not a code for ageing / senescence but only a code for senility /old age (797) among "Symptoms, signs and ill-defined conditions". Likewise, in the ICD-10 (http://www.who.int/classifications/apps/icd/icd10online/) there is only a code for senility / old age (R54) in the chapter XVIII, titled "Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)", paragraph "General symptoms and signs (R50-R69)", and therefore not including distinct diseases or physiological events. In fact, for current medicine and in official classifications, ageing as a distinct entity is nonexistent and old individuals never die by ageing but, in general, by one or more diseases typical of old age.
2) *Old individuals have tissues and organs that have been progressively impaired by a lot of different damaging factors, in particular oxidizing agents*. This thesis appears to ignore cell turnover and the experiments where cells in replicative senescence and with all the manifestations of cell senescence are transformed by telomerase activation into cells with unlimited replication capacities and without signs of cell senescence [151,152,153,154,155]. "... there is something fundamental controlling the occurrence or accumulation of cellular free radical damage, something controlling the balance between damage and homeostasis. Free radical damage accumulates in somatic cells, but homeostasis is a sufficient match in germ cell lines. Alteration in gene expression, modulated by telomere length, is a likely candidate for such control." [113] Oxidative damage becomes a problem when cell turnover

slackens and cell senescence increases: limits in the telomere-telomerase system are the primary cause and oxidative damage only a consequence [113].

3) *Ageing, being the consequence of numberless and random factors, is in principle not likely controllable and strong efforts could obtain only a slowing down of an inevitable process.* This is contrast with the evidence of the telomere-telomerase system, cell turnover, atrophic syndrome caused by cell turnover decline, and experiments documenting that at cell level senescence is totally reversible and avoidable [113].
4) *Ageing is something intrinsic to the condition of the living being, in particular of multicellular organisms, and therefore it is inevitable.* This is in plain contrast with the existence of many species that in the wild show no increase in mortality (e.g., rockfish, sturgeon, turtles, bivalves, etc. [111]) and defined, if with considerable life spans, "animals with negligible senescence" [98] or "ageless animals" (http://www.agelessanimals.org/). There are even species with mortality decreasing with age, e.g., depending on an increasing body size [112]. On the contrary, individuals of some unicellular eukaryotic species age, that is the telomere-telomerase system allows only a limited number of duplications (replicative senescence) and, in relation to the previous number of duplications, causes a decline in the overall functionality of the cell (cell senescence) with an increasing sensibility to apoptotic stimuli [122,123,124].
5) *Age-related increasing mortality, alias fitness decline, cannot be adaptive because natural selection favours individuals with greater fitness.* Natural selection favours genes with positive inclusive fitness, even with negative individual fitness [59,80,81,82,83], and, therefore, in principle a gene causing age-related fitness decline, that is negative individual fitness, could be favoured by natural selection in particular ecological conditions [21]. The existence, in the wild, both of species with fitness decline and of species without fitness decline are a demonstration that unavoidable universal senescence-causing factors are unlikely and that both cases are somehow adaptive. It is remarkable that replicative senescence and cell senescence in yeast are weighed as adaptive [20,127,128,129,130,131] and the logical consequence would be to accept as possible that the effects of the telomere-telomerase system in multicellular organisms are adaptive too.

Weight of Ageing for Life Span and Longevity

The effects of fitness decline on life span (mean duration of life, ML) and longevity are huge and often underestimated. For a species with a fixed mortality rate (λ), survivors at time t (Y_t) are given by the formula:

$$Y_t = Y_0 (1 - \lambda)^t \quad (10)$$

With $Y_0 = 1$, life span (ML) is:

$$ML = {}_{t=0}[(1 - \lambda)^t]^{t=h} = - \frac{1}{\mathrm{Log}_e(1 - \lambda)} \quad (11)$$

and the time t when Y_t individuals survive is:

$$t = \frac{\mathrm{Log}(Y_t)}{\mathrm{Log}(1 - \lambda)} \quad (12)$$

In USA, 2005 statistics say that for the total population the probability of dying between ages 20 to 25 and between ages 25 to 30 were 0.004869 and 0.004865, respectively, which is about 0.00097/year [205]. With $\lambda = 0.00097$, without the age-related mortality increase the life expectancy of 20-30 years old individuals ($ML_{20\text{-}30}$) would be about 1,030 years and 1% would be alive after 4,745 years.

Excluding accidents (unintentional injuries) and homicides, which caused in 2005 about half of the deaths for 20-30 years old individuals [205], that is roughly halving the value of λ to 0.0005, $ML_{20\text{-}30}$ would be about 1,999 years and 1% would be alive after 9,208 years!

The same statistics say that the probability of dying between ages 55 to 60 was 0.036299, which is about 0.00726/year [205], 7.45 times the mortality of 20-25 and 25-30 years cohorts. With this value $ML_{55\text{-}60}$ would be about 137 years and 1% would be alive after 632 years.

It must be underlined that an individual without an age-related increasing mortality rate would have an "unlimited longevity" but this should not be confused with the concept of "immortality" (infinite longevity and life span). In fact, an individual of a species with negligible senescence (ageless animal) or even of a species with age-related decreasing mortality (negative senescence [112]) dies by events that are mortal at any age (severe infections, accidents, predation, killing by other individuals of the same species, etc.; in short, extrinsic mortality) and, moreover, at ages when practically no individual survives in the wild for the extrinsic mortality and so there is no natural selection, if the individual survives because reared in protected conditions, it is possible the onset of unforeseeable and deadly internal imbalances. Therefore, a hypothetical man with no age-related increasing mortality should be in the condition of unlimited longevity but limited life span.

Interactions between Diseases of Different Categories and between Ageing and Diseases

Evolutionary interactions between diseases of different categories and between diseases and disease-like phenomena, in particular senescence, are important. For the sake of brevity, only some interactions will be outlined.

A. Interactions between Diseases Caused by Alterations of the Genotype (Category 1) and Ageing (Category 5.3.2)

Equilibrium frequency of a harmful gene C (C_e) and of its phenotypic expression (P_e) are both in inverse function of [s] (absolute value of the disadvantage s; see formulas 1-7), which

is depending on the reproductive value of the individuals damaged by C. In species with age-related fitness decline, as older individual have a smaller expectation of life and, therefore, a smaller reproductive value, if C damages older individuals, C_e and P_e will be greater than for another harmful gene damaging younger individuals, that is a disease caused by an alteration of genotype that manifests itself at older ages (e.g., Huntington's disease) is expected to have higher frequency.

In numerical terms, if a dominant harmful gene C kills (s = -1) at an age when in the wild (or in the ancestral condition) only 1% of the population survives and the frequency of mutation into C from neutral alleles is 0.00001, the frequency of the diseases (P_e) is expected to be:

$$P_e \approx 0.00001 / [0.01 \text{ H} -1] = 0.001 \quad (13)$$

The opposite concept, the hypothesis that age-related fitness decline is caused by the combined effect of many harmful genes acting at older ages and insufficiently eliminated by natural selection (mutation accumulation theory) is untenable because contradicted by theoretical arguments [10,13,21] and unsupported by empirical evidence.

B. Interactions between Diseases Caused by Interactions with Other Species (Category 3) and Ageing (Category 5.3.2)

A parasite damaging an older individual of a host species with age-related fitness decline, causes a disadvantage lower than a parasite damaging a younger individual, as older individuals have less reproductive value. Therefore, it is expected that older individuals will suffer from the effects of parasite actions more severely that younger individuals as natural selection is less effective when the reproductive value is lower. For humans, the greater gravity of infections in older individuals is well known and documented [195].

C. Interactions between Diseases Caused by Alterations of the Ecological Niche (Category 2) and Diseases Caused by Interactions with Other Species (Category 3)

The huge and continuous modifications of human ecological niche caused by technological innovations, urbanisation, demographic growth, changes of lifestyle, foods, hygienic habits, etc., have greatly altered the conditions to which the species is adapted. Fragile and intricate evolutionary balances between the man and his numerous parasites, attained after thousands of human generations (and millions of parasite generations) have been crushed with catastrophic results, worse than for any other human disaster or calamitous event, war included. Some examples:

1) The extraordinary growth of human population and of its demographic density, its aggregation in urban crowds with water polluted and habitations infested by infected

animals, the cohabitation or proximity with bred animals, dangerous hygienic habits, etc., have provoked from the ancient times dreadful epidemics (black death, bubonic plague, smallpox, typhus, cholera, influenza, hepatitis A, tuberculosis, HIV, etc.) with the deaths of hundreds of millions of men. From 1347 to 1640, Black Death, a disease probably different from bubonic plague [206] was the scourge of Europe and other parts of the world, with more than 100 millions of victims (Figure 17). In 1918-1920 a single epidemic of influenza (Spanish flu) killed perhaps 40-50 million people worldwide [207] or, according to current estimates, 50-100 millions [208], that is from 2 to 5 times the deaths caused by World War I in five years. When Europeans reached the America, they were selected, much more than American indigenous people, by centuries of terrible epidemics. The germs that they spread unintentionally in America were dangerous for them but very frequently lethal for indigenous populations, which were devastated by smallpox, measles, influenza and other diseases for which they had no evolutionary experience [209].

Figure 17. *The Triumph of Death* (black plague), a painting of Pieter Bruegel the Elder.

2) Statistical data show that alterations of the ecological niche and, on the other hand, corrections of these alterations are far more important of non-preventive medical treatment, antibiotics included. In fact, in USA infectious disease mortality rate has strongly declined before the introduction of sulphonamides and penicillin, and the usage of these drugs and of many new antibiotics has not changed sensibly the decline of mortality by infections [210]. In recent years, mortality by infections is increasing because of HIV diffusion and, perhaps, of increasing antibiotic resistance (Figure 18).

   Indeed, use and abuse of antibiotics and chemotherapeutic substances have selected antibiotic resistant bacteria with weighty consequences (about 90,000 U.S. residents

die each year by nosocomial infections [211]). Even vaccines, a medical triumph, if not properly planned or used, can "provoke and even be overcome by pathogen evolution" [212].

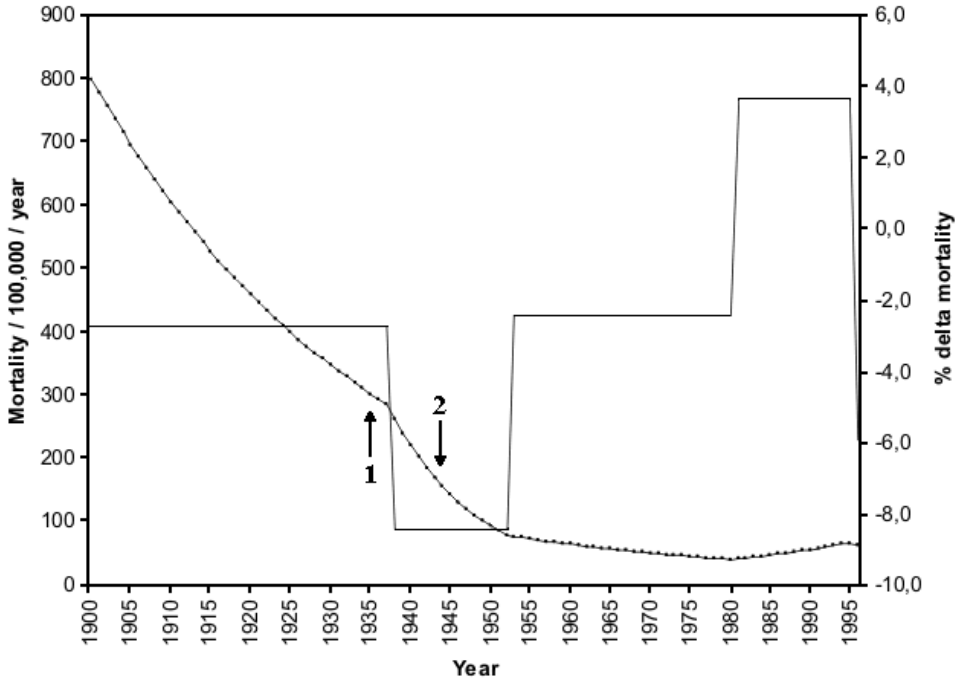


Figure 18. Overall trends in infectious disease mortality rate and per cent variation of mortality rate in USA from 1900 to 1996 [210]. The episodic strong increase in mortality due to 1918 influenza pandemic has been disregarded. Sulfonamids were released in 1935 (arrow 1) and the beginning of clinical use of penicillin was in 1943 (arrow 2) but there is no clear effect of their use on mortality rates.

3) Hygienic or iper-hygienic habits restrict and delay the first exposure to microbes and parasitic worms or make impossible infections or infestations. These modifications of the ecological niche, in principle always beneficial for traditional medicine, on the contrary for evolutionary medicine are potentially harmful and dangerous.

   Delayed exposure to poliovirus is a likely cause of modern epidemics of poliomyelitis, a scourge till worldwide application of polio vaccines [209]. Poliovirus has been for thousands of years an endemic pathogen, which rarely caused poliomyelitis or infantile paralysis, until the 1880s, when major epidemics of poliomyelitis began to occur in Europe and, soon after, in the United States [213].

   Reduced exposure to allergens, especially in early life, caused by modern extreme hygiene, is a significant risk factor for allergy and is the most likely explanation, at present, for the extraordinary worldwide increase in atopic allergy [51].

   "Hygiene hypothesis" maintains that exposure to bacteria, viruses and parasitic worms during childhood protects against the development of allergies [214] and atopic diseases [215]. Allergies may be caused by a delayed establishment of gut flora in infants [216].

For diabetes mellitus type 1, an autoimmune disorder, it is hypothesised that "... increased hygiene may contribute to an imbalance of the immune system, facilitating autoimmune reactions [against β-cells] when virus infections, or proteins like cow's milk or gluten, provoke." [217]

Some intestinal worms secrete chemicals that suppress the immune system to prevent the host from attacking the parasite [218] and without these substances the immune system becomes unbalanced and oversensitive [219]. Clinical trials have been initiated to test the effectiveness of certain worms in treating some allergies [220].

The deliberate infestation with a parasitic worm (helminthic therapy) is a promising treatment for several autoimmune diseases such as Crohn's disease [221,222,223], ulcerative colitis [223], multiple sclerosis [224], allergic asthma [220,225], etc., whose incidence is greatly increased in recent years and, moreover, is greater in industrialised countries in comparison with developing countries with less strict hygienic habits [225,226,227,228]. These autoimmune and allergic disorders, and others, are explained by the Hygiene hypothesis, which is in short a thesis of evolutionary medicine.

4) The abuse of soaps, deodorants, detergents, disinfectants, etc., modifies normal microbial flora of epidermis and external mucosae (especially of armpits, genitals and hands) and causes the spreading of pathogens, in particular fungi (personal observation).

D. Interactions between Diseases Caused by Alterations of the Ecological Niche (Category 2) and Ageing (Category 5.3.2)

Various alterations of the ecological niche and the diseases caused by them (cigarette smoking, diabetes mellitus, hypertension, hypercholesteremia, obesity, alcoholism, etc.; "risk factors") increase physiological cell turnover, likely provoking a greater apoptosis rate, and therefore accelerate the onset of manifestations that without them should be present only in older individuals [193]. The effects of risk factors are countered by drugs with organ protection qualities ("protective drugs") such as statins [193,229], ACE-inhibitors and sartans [230], probably by normalisation of apoptosis rate.

Risk factors increase the frequency of cardiovascular diseases and accelerate their onset [195]. Smoking, diabetes, and obesity are risk factors for AMD [231]. There is association between Alzheimer disease and risk factors [232].

Protective drugs reduce the risk of cardiovascular diseases [229,230] and of diabetes [233,234], are effective in the prevention of atrial fibrillation [235,236] and against Alzheimer disease [237].

Statins reduce decline in lung function [238] and lower the risk of nuclear cataract [239].

Some diseases caused by alterations of the genotype, such as Werner syndrome and dyskeratosis congenita have analogous effects of risk factors on cells with moderate and high turnover, respectively [182] (Figure 19).

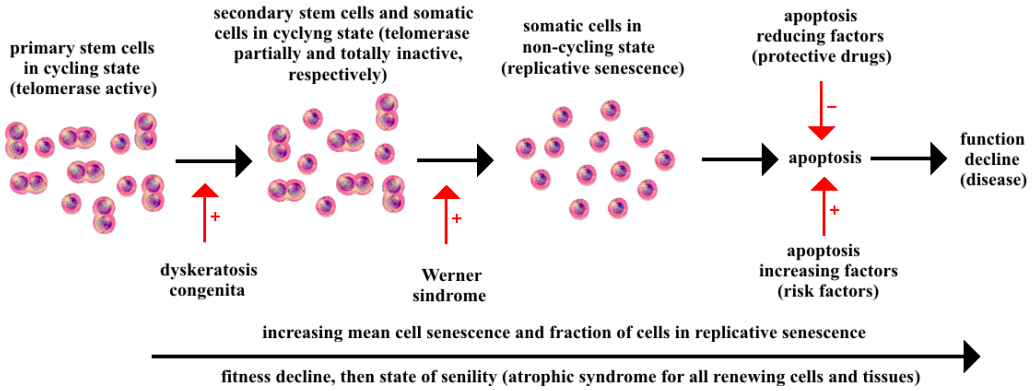


Figure 19. Risk factors (and some genetic diseases) increase apoptosis rate and cell turnover. Protective drugs counter the effect of risk factors but it is not documented the capacity of reducing physiological turnover rate.

Comparison between Evolutionary Disease Categories and the Breakdown Types of a Machine

It is possible a comparison between the various disease categories classified in evolutionary terms and the various types of breakdowns of a machine (e.g., a car) (Figure 20).

The industrialist is certainly very careful in its manufacture, but it is inevitable that some cars will be sold with one or more faults in construction. As for more frequent defects the manufacturer will adopt opportune measures, it is predictable that each particular defect will have a limited frequency. The breakdowns caused by these defects are analogous to the diseases caused by alterations of the genotype.

A car has a range of operative conditions, e.g., specific types of oil, lubricants and fuel to be used, particular maintenance operations to be observed, etc. The owners not observing manufacturer indications expose their cars to conditions for which the car is not designed and therefore they will risk failures. The breakdowns with these causes are analogous to the diseases caused by alterations of the ecological niche.

In their use, cars can collide with other motor-vehicles or be damaged by vandals. These harms are analogous to the diseases caused by interactions with other species.

If the owner uses the car on roads with gravely uneven surface or to cross a stream or for other conditions for which the car is by no means designed, it is probable a damage, which is analogous to the diseases caused by conditions beyond adaptation range.

As years go, the car wears out, breakdowns becomes more and more frequent, repairs more and more expensive and difficult, spare parts are of not easy finding, until the car is unusable and must be scraped. In part, this is due to mechanical wear and to some components that cannot be substituted (or with replacements too expensive). In part, this is because cars have a built-in obsolescence, that is they are designed not for the greatest duration but to last for a certain period after which the machine must begin to break down

with increasing frequency and with increasing costs for the owner until he is induced to buy a new machine. Built-in obsolescence and its consequences are analogous to ageing manifestations.

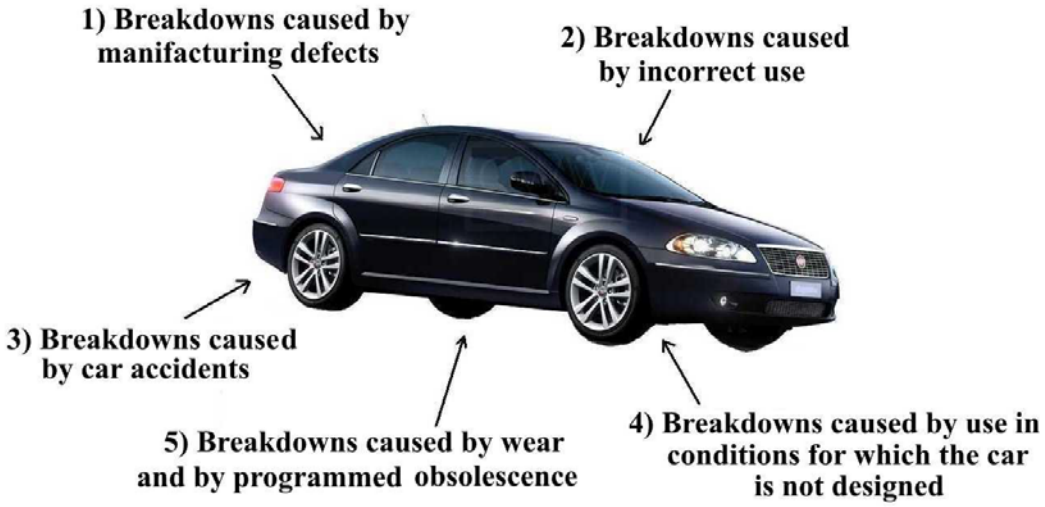


Figure 20. Categories of car breakdowns, in analogy with the evolutionary classification of diseases and the peculiar phenomenon of ageing.

The concept of planned or built-in obsolescence is less known and obvious than that of mechanical wear.

In 1983, I wrote:

"Built-in obsolescence is that characteristic of an industrial product, specifically planned and pursued, for which the product deteriorates and becomes more and more hardly repairable after a definite time, even though being reliable and fully usable before that time.

Built-in obsolescence causes a waste of materials and a considerable economic overload for the consumer, but has at least three important advantages.

The first is to avoid that the annual part of renewal of a product in a stable market be minimal. For example, a nation in which there are 10 millions of motor-vehicles, with a mean duration of ten years, demands for replacement an annual production of 1 million of motor-vehicles. If the mean duration of a car would increase to 20 years, the annual production should fall to 0.5 millions, with catastrophic consequences for proceeds and employment. The second advantage is the introduction of new technologies with speed inversely proportional to the mean duration of the product. A product with unlimited duration would delay or even make economically disadvantageous the use of new and more effective technologies. The third advantage is that a productive system organised for a quick and continuous renewal is easily adaptable to: a) an unexpected market growth; b) the opening of new markets; c) the conversion to the production of other items; d) the transformation in military industry, etc. On the contrary, the production of goods with very long duration, as there is a minimal annual production, is not much fit to the aforesaid events.

In this regard, I have the following beliefs.

Built-in obsolescence is a hidden pillar of the modern “consumer culture”. Neither manufacturers nor trade unions, nor politicians have interest to publicise such pillar.

The consumer believes that it is not possible to make products with greater duration or that the necessary modifications would render the product too expensive. These opinions are wrong and on the contrary considerable efforts in the design of an industrial consumer product are directed to make the product both accurate and reliable until a certain time and afterwards not much reliable and more and more expensively repairable.

Built-in obsolescence of an industrial product and the programmed senescence of a living being are two very different phenomena, yet the analogies are considerable and not superficial. With opportune modifications of the terms, the main common aim is that to allow to the industrial product or to the living being the greatest evolution, the greatest adaptability to new conditions, the greatest competitiveness in the struggle.

If the considerations stated regarding senescence are true:

It is tragic to observe that the man and his machines share a last fate similar in its essence.

It is ironic to consider that the modern technology even in this has been preceded and exceeded by the Nature.

It is incredible that in a civilisation in which built-in obsolescence is fundamental, it is not known that the living world obeys to a parallel logic” (translated from Italian [10]).

From Wikipedia (14/08/2008) Article: Planned Obsolescence

“Planned obsolescence (also built-in obsolescence in the United Kingdom) is the process of a product becoming obsolete and/or non-functional after a certain period or amount of use in a way that is planned or designed by the manufacturer. Planned obsolescence has potential benefits for a producer because the product fails and the consumer is under pressure to purchase again, whether from the same manufacturer (a replacement part or a newer model), or from a competitor, which might also rely on planned obsolescence. For an industry, planned obsolescence stimulates demand by encouraging purchasers to buy again sooner if they still want a functioning product. Built-in obsolescence is in many different products, from vehicles to light bulbs, from buildings to software. There is, however, the potential backlash of consumers who learn that the manufacturer invested money to make the product obsolete faster; such consumers might turn to a producer, if any, which offers a more durable alternative.

Planned obsolescence was first developed in the 1920s and 1930s when mass production had opened every minute aspect of the production process to exacting analysis.

Estimates of planned obsolescence can influence a company's decisions regarding product engineering. Therefore, the company can use the least expensive components that satisfy product lifetime projections. Such decisions are part of a broader discipline known as value engineering.

The use of planned obsolescence is not always easy to pinpoint, and it is complicated by related problems, such as competing technologies or creeping featurism, which expands functionality in newer product versions.

- Rationale behind the strategy

A new product development strategy that seeks to make existing products obsolete may appear counter intuitive, particularly if coming from a leading marketer of the existing products. Why would a firm deliberately endeavour to reduce the value of its existing product portfolio?

The rationale behind the strategy is to generate long-term sales volume by reducing the time between repeat purchases (referred to as shortening the replacement cycle). Firms that pursue this strategy believe that the additional sales revenue it creates more than offsets the additional costs of research and development and opportunity costs of existing product line cannibalization. However, the rewards are by no means certain: in a competitive industry, this can be a risky strategy because consumers may decide to buy from competitors. Because of this, gaining by this strategy requires fooling the consumers on the actual cost per use of the item in comparison to the competition.

Shortening the replacement cycle has many critics as well as supporters. Critics such as Vance Packard claim the process wastes resources and exploits customers. Resources are used up making changes, often cosmetic changes, that are not of great value to the customer. Supporters claim it drives technological advances and contributes to material well-being. They claim that a market structure of planned obsolescence and rapid innovation may be preferred to long-lasting products and slow innovation. In a fast paced competitive industry, market success requires that products are made obsolete by actively developing replacements. Waiting for a competitor to make products obsolete is a sure guarantee of future demise ..."

An Example of Difference between the Current Classification of Diseases and the Evolutionary Classification

Some subjects suffer in juvenile age from myocardial infarction or cerebral ischemia as outcome of serious hereditary hypercholesteremia or other genetic diseases. Others, smokers and/or obese and/or diabetic and/or hypertensive middle-aged subjects, are hit by the same affections. Others, non-smokers non-obese non-diabetic old subjects, suffer from the same diseases.

In the traditional classification, the three groups of patients are classified together, while in the evolutionary classification their affections are divided in three distinct groups of diseases.

It being understood that the aforesaid diseases in their manifestations are treated in the same way, in the evolutionary classification there is a clear-cut distinction.

In the first case, we have diseases deriving from alterations of the genotype: practically they are not preventable (with the exception of therapeutic abortion that is not exactly a

prevention), it is possible a precocious identification, pharmacological treatment reduces the risk, ideal therapy is genetic, ideal prevention is eugenics before conception.

In the second case, we have diseases deriving from alterations of the ecological niche. Effective prevention is possible and should be the best choice. Pharmacological treatment reduces the risk of new events but the correction of ecological niche alterations should be the main measure.

In the third case, we have diseases deriving from a physiological function as ageing appears to be. Prevention is not possible. Pharmacological treatment could reduce but not cancel the risk, which increases with the age. The only effective measure could be a genetic modification of ageing regulating and determining mechanisms.

Strategies to Reduce Morbidity Rates and to Increase Life Span and Longevity

1. Actions for the First Evolutionary Category of Diseases (Caused by Alterations of the Genotype)

Today: If possible, precocious identification of subjects with genetic diseases and their pharmacological treatment. Therapeutic abortion in some cases.

In the future:

Option A - Overcoming the limits of current gene therapy [240], in particular the transitory success of the therapy, caused by cell turnover if the corrected gene is not inserted in stem cells, and the possibility that an insertion may inactivate a suppressor oncogene and arouse a cancer (insertional oncogenesis) [241] (Figure 21), development of methods with which it will possible to insert in a sure way in the genome of the patient the corrected gene in a position not causing possible dangerous interference with other genes. Treatment of genetic diseases with gene therapy, in a way that the therapeutic method is unvarying and only the genetic inserted sequence changes. Limitation of the reproduction of subjects with genetic alterations, subordinating the reproduction to controls, if possible, of the genetic condition of the foetus.

Option B - Development of methods with which it will possible to substitute in a sure way the altered gene with the corrected gene in the genome of the patient and in all his cells, germinal cells included (Figures 22 and 23). Reproduction without restrictions as long as it is verified that the substitution has been made correctly.

Effects: Limitation of morbidity and mortality deriving from genetic diseases. Limitations of the progressive increase in their incidence in the future generations. Limited increase in the mean duration of life. No increase in longevity.

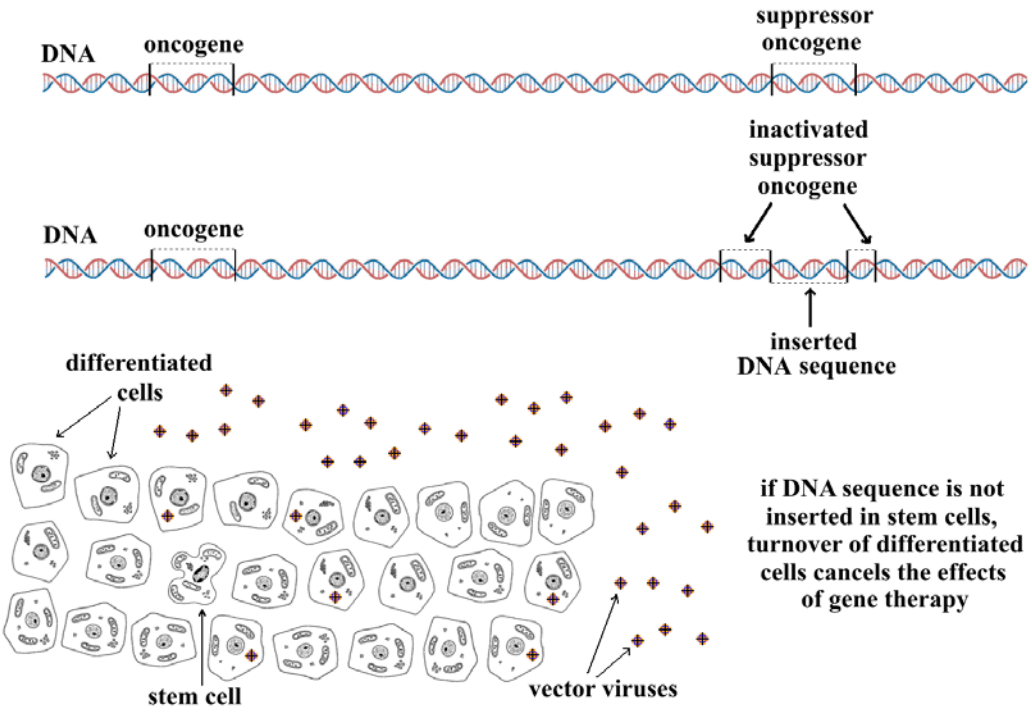


Figure 21. Current gene therapy. DNA sequence is inserted in a random position by a vector virus. If an insertion inactivates a suppressor oncogene, this may cause a cancer. The type of vector virus and/or limits in the dose of viruses inoculated may cause the transformation only of differentiated cells and not of the rare stem cells and, consequently, the transitory success of the therapy, because cell turnover gradually substitutes differentiated cells with new cells originated from non-transformed stem cells.

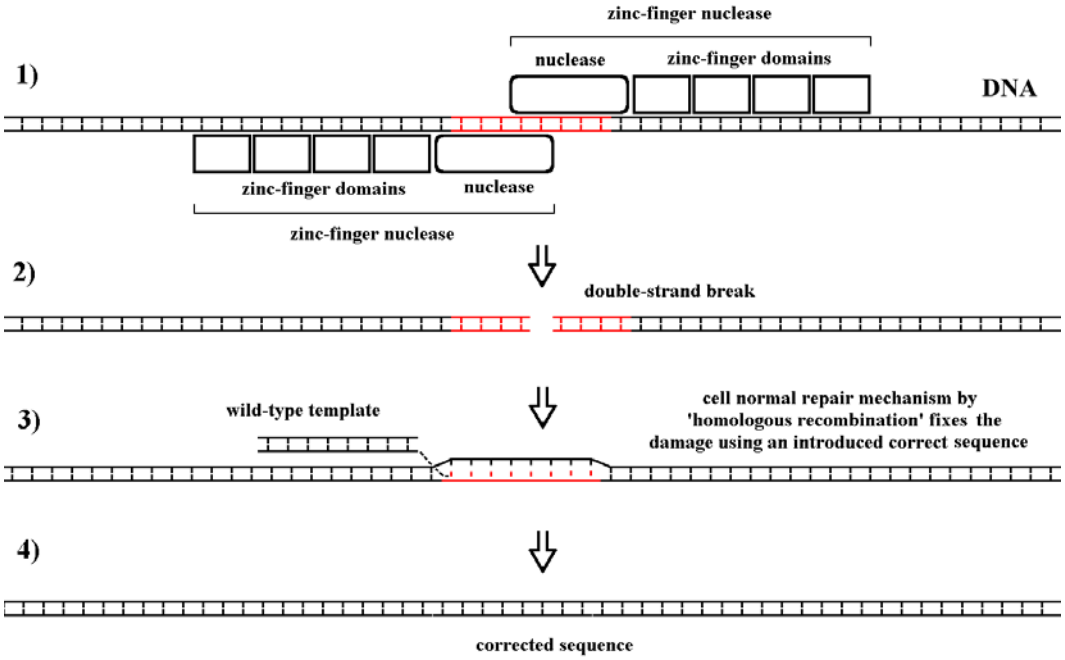


Figure 22. Option B. The corrected gene is inserted in substitution of the altered gene. With the use of two zinc-finger nucleases, composed of zinc-finger domains (each specific for a particular three-base DNA sequence) and a nuclease (a Type IIS restriction enzyme), it is possible to break DNA double-strand in a precise point with the successive correction by normal cell DNA-repair system by using an introduced DNA corrected sequence [242]. This method appears very promising [243].

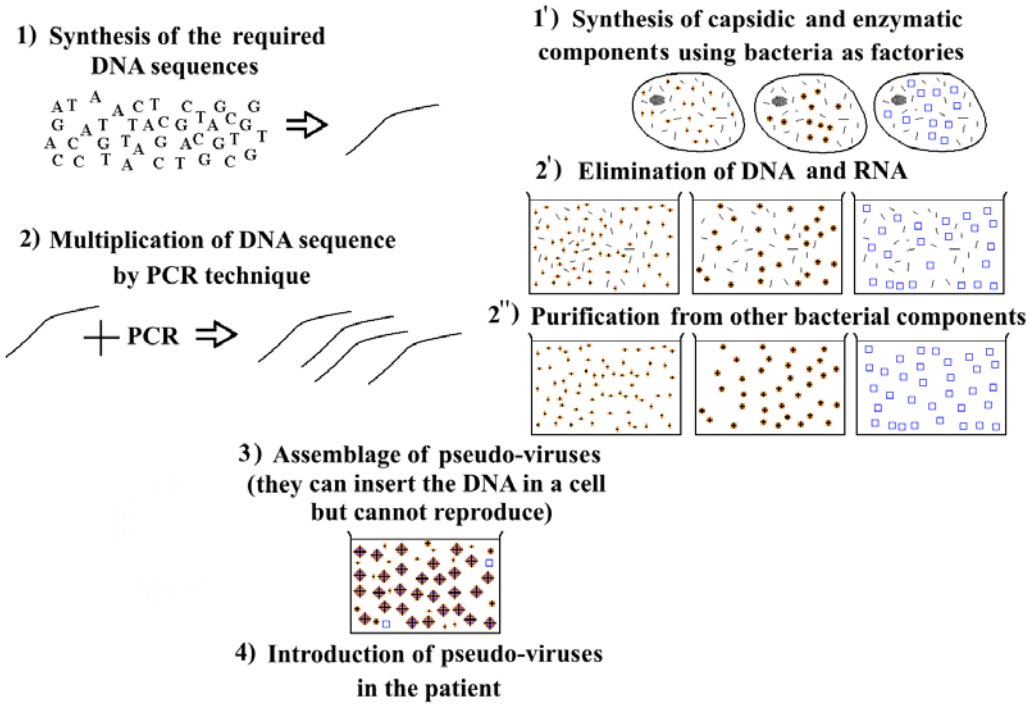


Figure 23. Creation of gene vectors (hypothetical scheme). The required DNA sequences (for the specific zinc-finger nucleases, for the gene to be modified, etc.) are created starting from defective viral sequences and from single nucleotides and multiplied by using PCR technique. Capsidic components and enzymes essential for the assemblage and activation of pseudo-virus are synthesised by using transformed bacteria and later eliminating DNA, RNA and other bacterial components. DNA sequence and capsidic and enzymatic components are assembled creating pseudo-viruses able to insert or substitute a DNA sequence in a cell but not to reproduce.

2. Actions for the Second Category of Diseases (Caused by Alterations of the Ecological Niche)

Today: Generally, after the manifestation of the disease, it is strongly advised to avoid risk factors. The people and many physicians have not a precise knowledge of the risk factors. The affection is defined disease and there is not a full awareness that the pathological condition is the alteration of the ecological niche.

In the future: Optimal knowledge of the ecological conditions to which our species is adapted. It is necessary to define the risk for each alteration of the ecological niche and to spread in the population and the medical categories the knowledge of the risks. Prevalent utilisation of the resources for prevention. Adoption of measures discouraging risk behaviours. The cures for subjects not observing preventive measures and advice must be the last bastion.

Effects: Drastic reduction of all the pathologies classifiable in this category with parallel reduction of morbidity and mortality. Reduction of the related sanitary costs. Increase in life span. No increase in longevity.

3. Actions for the Third Category of Diseases (Caused by Interactions with Other Species)

Today: Indiscriminate actions against any type of infection or parasitosis. Excessive or inappropriate use of antibiotics. Scarce attention to the ancestral ecological relationship between man and microbial species and parasites.

In the future: Widening of the study of the relations between man and his parasites. Reduction or elimination of the circumstances that increase the danger of parasitic infection and epidemics. Limits in the excessive or inappropriate use of antibiotics. A greater and prevalent use of preventive measures and vaccines.

Effects: Reduction of morbidity and mortality. Reduction of antibiotic-resistance cases. Increase in life span. No increase in longevity.

4. Actions for the Fourth Category of Diseases (Caused by Conditions beyond Adaptation Range)

Today: Actions that reduce risk conditions.

In the future: More careful actions to reduce risk conditions (e.g., safer cars and roads, greater severity and observance of safety measures at work, etc.)

Effects: Reduction of morbidity and mortality. Increase in life span. No increase in longevity.

5. Actions for Ageing

Today: Ageing is considered not a physiological event but a mixed set of diseases with age-related increasing frequency and severity. Ageing manifestations are empirically treated for their dysfunctions and in analogy with diseases showing the same dysfunctions. The cures allow often an increase in survival time in conditions of low quality of life.

In future: It is indispensable to acquire the awareness that ageing is something other than a disease phenomenon and that needs specific measures. It is possible to conceive an ambitious project for the solution of the problem in four steps:

Step 1

Parallel pursuit of various targets (duration: at least a decade)

a) Widening of the studies on the telomere-telomerase system;
b) The same for apoptosis phenomenon;

c) The same for cell turnover of all tissues and its effect on the functions of the organs;
d) The same for the morphogenesis of the organs, in particular for the dentition;
e) Development of genetic techniques for the effective and precise insertion of a genetic sequence in a point of the genome not causing dangerous alterations;
f) Development of genetic techniques for the effective and precise substitution of a genetic sequence with another sequence;
g) Research of possible safe drugs to modify the telomere-telomerase system and/or cell turnover (or other) so that longevity is increased.

Step 2

Parallel pursuit of various targets (duration: at least a decade)

a) Experiments on animals of insertion of genetic sequences to modify the modulation of the telomere-telomerase system for increasing longevity;
b) The same with techniques of genetic substitution;
c) First applications of the above-mentioned techniques for the treatment of severe genetic diseases;
d) First applications of the above-mentioned techniques for the treatment of age-related severe diseases such as age-related macular degeneration and Alzheimer's disease;
e) As with (a) and (b) to obtain multiple dentitions;
f) Experiments on animals of possible drugs with increasing longevity qualities.

Step 3

Duration: at least two decades

a) First experiments on man of gene therapy (but not on germinal cells) and of possible drugs with increasing longevity qualities;
b) Verification of the results and progressive widening of the experiments.

Step 4

Duration: indeterminate

a) Possible experimentation and application of gene therapy on human germinal cells;
b) Applications on a large scale of safe and tested techniques and drugs

Effects: Increase in the mean duration of life deriving from longevity increase.

For the extreme weight of the argument, the creation of an apposite international agency, adequately funded, could be useful, with the specific aim of controlling ageing and, as a very important corollary, genetic diseases, following the example and the wonderful outcomes of NASA (Figure 24).

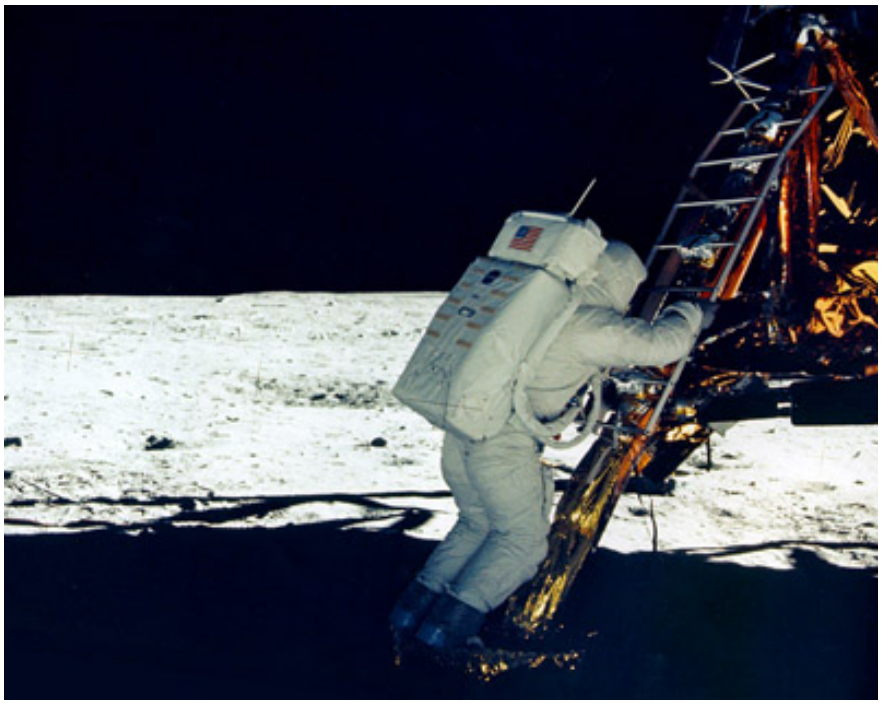


Figure 24. President John F. Kennedy focused NASA, founded in 1958 by Eisenhower, on sending astronauts to the moon by the end of the 1960s. This aim was achieved on July 20, 1969 (from NASA official site http://www.nasa.gov/).

Characteristics of a Future Age with Unlimited Longevity

When Moses, by then very old and just before his death, saw from the mountain of Nebo the Promised Land [Deuteronomy, 34], certainly the Hebrews wept for joy and imagined the ending of all their torments. However, the Promised Land, though ending the many pains they had suffered in Sinai, was the beginning of many other sufferings, struggles and disillusions.

A world with unlimited longevity would be as the Promised Land: many pains of today would end, but many others would begin. Our descendants would commiserate with us for our limited life span and longevity but would envy us for so many other things.

A society composed of individuals with very long longevity cannot be in a simple way the same society of today. All or most would have to change.

A very small risk to life considered today acceptable because the expectation of life is a few decades becomes unacceptable if there is a very long expectation of life. Rigorous measures to prevent incidents—with a severity currently unimaginable—would be the rule.

Today, procreation is free and one of the rights considered inviolable. The limitation of only one child per family imposed in China seems to most people an unacceptable limitation. In a society with a very long life span, births would be regulated and limited in proportion. Children would be a rare exception, cuddled and protected by whole communities. Motherhood would become a rare privilege.

Today, marriage is a life-long oath and its break is a trauma strongly discouraged. Marriage would be transformed into a temporary engagement with specific rules and limitations.

Powerful and/or rich persons would be able to obtain peaks of power and/or wealth today inconceivable. Many rules would be arranged to limit the excesses and to assure turnover in power management.

Today, a man studies for a certain period of his life, then works for another period and then retires on a pension, enjoying the fruits of his work. This way of life would not be possible any longer. Perhaps there would be an alternation between periods of work and others of rest or study.

The mean level of education would increase enormously, and cases of persons with various degrees and specialisations would be frequent as well, because after a certain period there would be a psychological demand to change the object of study and work.

There would be extreme attention to beautiful, artistic and poetical things, and there would be supreme examples of lovers of artistic disciplines, but also monstrous examples of egoism and wickedness.

But there would be also the spread of what the Romans called *tedium vitae*, and perhaps suicide would become the main cause of death.

The wars—in memory—would become a symbol of extreme madness, but the world would be static and uniform. Our descendants would commiserate with us for our innumerable wars and yet in historical action representations would pursue those emotions that they would lack entirely in everyday life—a little like when we deplore the troubles of the past centuries but are fascinated by representations of warriors fighting with swords, bows and other ancient weapons.

And what are we to say of philosophy, religion, politics, poetry, sociology, psychology, etc.? All changes if the expectation of life is immensely great.

Cynics and unbelievers would state that God, religion and philosophy are reformulated and adapted to the new society, showing once again to be only creations of the human mind.

Mystics and believers would state instead that God, religion and philosophy are unchanged in their essence and that a life unlimited in its duration allows a better level of comprehension, because we would be less limited by physical ties.

Economics and politics would have radically different aims. Today, we plan for the contemporary generation and a little—if one is farsighted—for the next. In the future, men would think first to the future, as the contemporary generation would have to live in that time.

Conclusion

The development and the efficacious application on a large scale of safe techniques of gene therapy would reduce the consequences of diseases of category 1 (diseases caused by alterations of the genotype).

Respect for the ecological conditions to which the human species is adapted would largely reduce morbidity and mortality of diseases of category 2 (diseases caused by alterations of the ecological niche).

A better comprehension of the interactions between our species and its parasites and of the ecological conditions that minimise their damage, a greater use of vaccines and a more intelligent use of antibiotics would relieve the impact of diseases of category 3 (diseases caused by interactions with other species).

Strong precautionary measures would reduce the impact of diseases of category 4 (diseases caused by conditions beyond adaptation range).

Improvements in health cures and greater social assistance would improve the survival and the quality of life of elderly persons.

The entirety of the aforesaid measures would increase the mean duration of life, but longevity would be unvaried (Figure 25), except for a greater survival in very bad conditions of older persons.

A modification of our genetic program in the part that limits longevity would increase life span and longevity without a theoretical limit. It will be essential to make decisions regarding the ethical nature and advisability of this possibility, but here there is a boundary between science and politics, religion and human free will.

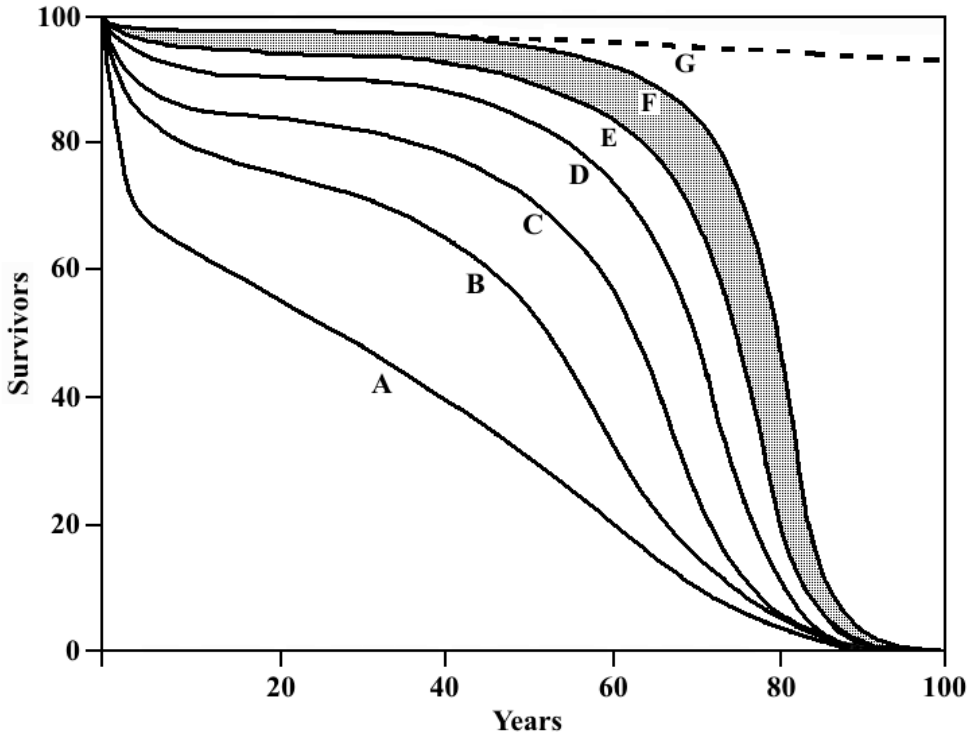


Figure 25. Life tables of human species (inspired by Figure 0.1 in [244]) illustrating a historical progressive increase in life span while longevity appears unchanged (curves A-E). Actual condition in developed countries is roughly indicated by curve E. With good preventive measures and better health treatment curve F is a likely outcome, with a little further increase in life span (dashed area) but not in longevity. Only with a modification of the progressive increase in mortality caused by intrinsic factors (ageing) will a drastic increase in life span and longevity be possible (curve G).

Appendix: Calculation of Equilibrium Frequencies

C is a gene having an advantage or disadvantage s in the homozygous condition and s' in the heterozygote condition. C' is its inactive allele. The notations C_n and C'_n indicate the frequency at the n-th generation of C and C', respectively. The frequency of mutation of C' in C is indicated with v and that of C in C' with u.

The frequencies of C_{n+1} and C'_{n+1} are given by:

$$C_{n+1} = \frac{C_n + C_n^2\, s + 2\, C_n\, C'_n\, s' + C'_n\, v - C_n\, u}{T} \qquad \text{(A1)}$$

$$C'_{n+1} = \frac{C'_n + 2\, C_n\, C'_n\, s' - C'_n\, v + C_n\, u}{T} \qquad \text{(A2)}$$

where T is the sum of numerators.

Formula (A1) can be written as:

$$C_{n+1} = \frac{C_n\,[1 + C_n\, s + 2\,(1 - C_n)\, s' - v - u] + v}{1 + 4\, C_n\, s' + C_n^2\,(s - 4\, s')} \qquad \text{(A3)}$$

There is equilibrium condition when the frequency of C does not change passing from a generation to the next, that is, when:

$$C_{n+1} = C_n = C_e \qquad \text{(A4)}$$

Substituting in (A3), we have:

$$C_e\,[1 + 4\, C_e\, s' + C_e^2\,(s - 4\, s')] = C_e\,[1 + C_e\, s + 2\,(1 - C_e)\, s' - v - u] + v \qquad \text{(A5)}$$

The solutions of this third grade equation are long and complex.

With a recessive harmful gene (s' = 0), supposing the simplification: $s < 0$; $u = 0$, formula (A5) becomes:

$$C_e\,(1 + C_e^2\, s) = C_e\,(1 + C_e\, s - v) + v \qquad \text{(A6)}$$

and the solutions are:

$$1,\ -\sqrt{-v/s},\ \sqrt{-v/s} \qquad \text{(A7)}$$

Discarding solutions 1 and 2 and recalling that $s < 0$, we can write:

$$C_e = \sqrt{v/[s]} \qquad \text{(A8)}$$

where [s] means the absolute value of s.

For Hardy-Weinberg equilibrium (CC + 2 CC' + C'C' = 1), the equilibrium frequency of the phenotype expressing the disadvantageous condition will be:

$$P_e = C_e^{\,2} = v/[s] \qquad \text{(A9)}$$

In the case of a dominant harmful gene, with the simplification: s = s' < 0; u = 0, formula (A5) becomes:

$$C_e\,(1 - 3\,C_e^{\,2}\,s + 4\,C_e\,s) = C_e\,(1 - C_e\,s + 2\,s - v) + v \qquad \text{(A10)}$$

and the solutions are:

$$1, \quad \frac{2\,s - 2\,\sqrt{s^2 + 3\,s\,v}}{6\,s}, \quad \frac{2\,s + 2\,\sqrt{s^2 + 3\,s\,v}}{6\,s} \qquad \text{(A11)}$$

Discarding solutions 1 and 2, and by considering that s = -[s]:

$$C_e = \frac{2\,s + 2\,\sqrt{s^2 + 3\,s\,v}}{6\,s} = \frac{1 - \sqrt{1 - 3\,v/[s]}}{3} \approx 0{,}5\,v/[s] \qquad \text{(A12)}$$

For Hardy-Weinberg equilibrium, the equilibrium frequency of the phenotype expressing the disadvantageous condition (P_e) will be:

$$P_e = C_eC_e + 2\,C_e\,C'_e = 2\,C_e - C_e^{\,2} \approx 2\,(0.5\,v/[s]) - (0.5\,v/[s])^2 \approx v/[s] \qquad \text{(A13)}$$

that is, for a dominant harmful gene the frequency of the phenotype is almost identical to that for a recessive gene.

In the case of a gene harmful in the recessive condition (s < 0) and advantageous in the heterozygote condition (s' > 0), with the simplifications u = 0; v = 0, formula (A5) becomes:

$$C_e\,[1 + 4\,C_e\,s' + C_e^{\,2}\,(s - 4\,s')] = C_e\,[1 + C_e\,s + 2\,(1 - C_e)\,s'] \qquad \text{(A14)}$$

and the solutions are:

$$0, \quad 1, \quad -\frac{2\,s'}{s - 4\,s'} \qquad \text{(A15)}$$

The first solution is valid if s < 0 and s' < 0. The second solution is valid if s > 0 and s' <= 0. The third solution is valid if s' > 0. Therefore, discarding solutions 1 and 2:

$$C_e = -\frac{2\,s'}{} = \frac{2\,s'}{} \qquad \text{(A16)}$$

$s - 4\,s'$ $[s] + 4\,s'$

For Hardy-Weinberg equilibrium, equilibrium frequencies of phenotypes in homozygous and heterozygote conditions are given by C_e^2 and $2\,C_e\,(1- C_e)$, respectively.

For chromosome alterations, it is useful to consider a chromosome alteration as an altered gene in a haploid organism, underlining that equilibrium frequency of a chromosome alteration (C_e) and equilibrium phenotypic frequency (P_e) coincide.

Therefore, supposing $s < 0$ and $u = 0$:

$$C_{n+1} = \frac{C_n - C_n\,s + (1 - C_n)\,v}{C_n - C_n\,s + (1- C_n)\,v - (1 - C_n)\,v} = \frac{C_n\,(1 - s - v) + v}{1 - C_n\,s} \qquad \text{(A17)}$$

$$C_e\,(1 - C_e\,s) = C_e\,(1 - s - v) + v \qquad \text{(A18)}$$

The solutions are:

$$1, \quad -v/s \qquad \text{(A19)}$$

that is: $C_e = P_e = v/[s]$ (A20)

as for P_e of recessive or dominant genes in a diploid organism.

Reviewed by

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