# A

## Aging Pathology

Giacinto Libertini
ASL NA2 Nord, Italian National Health Service, Frattamaggiore, Italy
Department of Translational Medical Sciences, Federico II University, Naples, Italy

### Synonyms

Aging diseases; Disease phenomena in the elderly; Geriatric diseases; Senile diseases

### Definition

There are diseases that are not typical of the old age or that manifest themselves starting from non-older ages and tend to worsen in relation to age. Excluding these diseases, there are others that, apart from particular exceptions with early onset, are characteristic of the elderly. "Aging pathology" means the study of these diseases that are typical of old age and in particular the study of the general phenomena that are their primary causes.

### Overview

Aging phenomenon, i.e., age-related progressive fitness decline, is explained in two completely different ways (Libertini 2015).

For the first, "nonadaptive aging paradigm", aging is a varied set of degenerative processes that are unified for convenience under one name. This view is prevalent and is officially reflected in the International Classifications of Diseases (ICD) where there is no distinct code for aging (WHO 2016, 2018), although in the section "General Symptoms," there is the code R54 for "senility" (WHO 2016) or the code MG2A for "old age" (WHO 2018), in the meaning of "old age/senescence without mention of psychosis" (WHO 2016, 2018). In paradoxical terms, according to this conception, though it is possible, and frequent, that one can die as a result of the degenerative processes that constitute aging, nobody might die as a result of aging. As a matter of fact, in WHO official world statistics no death is attributed to aging (Wikipedia 2017).

According to the first conception, talking about aging "pathology" is not appropriate in the strict sense. In fact, if aging is a set of pathological degenerative processes, any accentuation of these degenerative processes is not a distinct disease but only an early or more severe form of one or several of these degenerative processes. Nevertheless, within this conception, we could define as pertaining to aging "pathology" the cases in which one or several of these degenerative processes are more precocious or intense or the cases in which they assume peculiar characteristics that may be associated with manifestations not present in normal aging.


D. Gu, M. E. Dupre (eds.), *Encyclopedia of Gerontology and Population Aging*,
https://doi.org/10.1007/978-3-319-69892-2_33-1

In the opposite second interpretation ("adaptive aging paradigm"), aging is a specific physiological phenomenon, favored by natural selection at supra-individual level and with distinct mechanisms that determine it. This implies that aging, in addition to having its specific physiology, must necessarily have its own particular diseases (Libertini 2017).

Therefore, the discussion of the argument of this entry takes a double and somewhat different meaning, and appropriate distinctions will be expressed where necessary.

The pathological forms of aging are substantially of two types, depending on the causes that are at their origin (Libertini 2017): (1) Some alterations of the ecological niche to which our species is adapted, in particular alterations of the lifestyle, cause an acceleration and a worsening of the phenomena that characterize aging; and (2) some genetic alterations cause an acceleration and a worsening of aging phenomena or cause specific syndromes that show a marked intensification and deformation of parts of aging phenomena often with different peculiar characteristics.

In both interpretations of aging, it is necessary to distinguish these pathological expressions of aging from (i) the alterations present in normal aging and (ii) the diseases that are present at any age (e.g., infectious diseases and traumas) even though considering that they may have a different course for the greatest vulnerability to any harmful agent which characterizes aging.

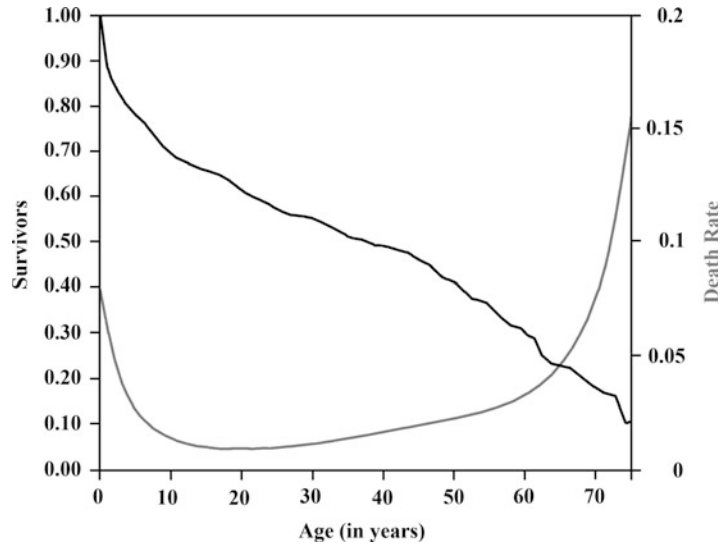
## Normal Aging

The study of a population in the wild allows the description of aging without the possible alterations caused by captive or civilized conditions. For our species, this is particularly difficult because populations living in primitive conditions are very few and vanishing. Moreover, when isolated people come into contact with modern populations, they suffer from a very high mortality caused by infectious diseases to which they are not adapted. Overcoming these great difficulties, the best study was conducted in Paraguay on an Ache population (Hill and Hurtado 1996) and allowed to make important observations not contradicted by other studies on populations under primitive conditions (Libertini 2013).

For the Ache people in wild conditions, i.e., before the contact with the researchers:

1. The mortality rates and the life table are shown in Fig. 1. "It is noteworthy the fact that, at ages 60 and 70 years, approximately 30% and 20%, respectively, of Ache survived" (Libertini 2013, p. 1024).
2. The causes of death are highlighted in Table 1. The vast majority of deaths were caused by violent causes
3. There were no reported cases of heart attack, stroke, diabetes mellitus, hypertension and many other diseases afflicting modern populations. In particular, no case of neoplasia was described (Hill and Hurtado 1996), although it is possible that someone of the older subjects was affected by a cancer or had died because of it.

It is worth noting that, for Ache people in wild conditions, the main causes of death for modern populations are absent, and the age-related increasing mortality appears related to a lesser capacity to avoid or counter violent causes of death. In the wild, when the reduction in physical capacities of an Ache reached a critical level and he/she was no longer able to hunt or harvest food or move with sufficient efficiency, he/she was simply left to himself/herself. However, the survival of almost 20% of the Ache at the age of 70 indicates that at this age many individuals were still capable of a self-sufficient life under natural conditions. It should also be noted that being malignant neoplasms a marginal or absent cause of death in natural condition and a tardy cause of death in comparison with the age-related mortality increase: "This completely disproves the hypothesis that the reduction of cell duplication capacities would be a defence against cancer: it would be like arguing that a defence against a deadly disease has the effect of mass-killing before the disease begins to kill!" (Libertini 2013, p. 1029).




**Aging Pathology, Fig. 1** Life table and probability of death in function of age for Ache people in wild conditions (forest period). (Data from Hill and Hurtado 1996)

## Aging Pathologies Caused by Alterations of the Ecological Niche

A species is adapted to the natural conditions in which it has evolved (ecological niche of the species). When these natural conditions suddenly change, the species is not necessarily adapted to the new conditions, and the "mismatch" between adaptation of the species and new conditions of life is a possible and probable cause of illness (Eaton et al. 1988; Libertini 2009a).

A "mismatch" may cause illness at early ages but also in later ages, determining, among other things, acceleration and alterations of normal aging. Here, it is opportune to specify that the term "normal" indicates the pace and characteristics of aging under natural conditions or in the absence of harmful changes in the ecological niche.

For the sake of brevity, a detailed discussion about mismatch effects on our health (see (Libertini 2009a)) would be impossible here. Table 2, based on a large set of references, shows that a series of age-related alterations of tissues or organs are worsened by risk factors such as diabetes, obesity/dyslipidemia, hypertension, smoke, alcohol abuse, and all conditions determined by unhealthy habits that are changes of the ecological niche and cause clear mismatches. It should be noted that a moderate use of alcohol does not appear to be a risk factor. Moreover, the negative effects of these risk factors are often countered by some types of drugs which, on the other hand, do not appear to have any effect on the physiological rhythms of aging (Libertini et al. In press).

With regard to the meaning of the second column of Table 2, it is necessary to underline that for programmed aging paradigm, the age-related dysfunctions depend on cell senescence and on the slowing down of cell turnover (Fossel 2004; Libertini 2009b). However, for cells that do not have cell turnover (perennial cells, e.g., many types of neurons), the age-related dysfunctions depend on cell senescence and on cell turnover decline of satellite cells of the perennial cells (Libertini and Ferrara 2016a).

For some relations reported in the table (beneficial effect of smoking on Parkinson's disease, emphysema inversely related to obesity/dyslipidemia, statin-induced damage to muscle and liver cells, slight increase in diabetes cases caused by statins) that are in contrast to the general patterns showed by other relations, possible justifications are proposed in the original work (Libertini et al. In press).

**Aging Pathology, Table 1** Causes of death for Ache people in wild conditions

| **In children aged 0–3 years** | | | **In children aged 4–14 years** | | |
|---|---|---|---|---|---|
| **Violence and accidents** | | | **Violence and accidents** | | |
| Homicide/neglect | 52 | | Homicide/neglect | 17 | |
| Captured/shot by Paraguayan | 21 | | Captured/shot by Paraguayan | 56 | |
| Accidents | 3 | | Accidents | 11 | |
| Total: | 76 | 58.02% | Total: | 84 | 84.85% |
| **Infections/intoxications** | | | **Infections/ intoxications** | | |
| Various causes | 36 | | Various causes | 11 | |
| Total: | 36 | 27.48% | Total: | 11 | 11.11% |
| **Congenital causes** | | | **Other causes** | | |
| Unspecified newborn death / defective | 17 | | Sick (unspecified)/sick in lungs | 4 | |
| Childbirth/mother had no milk | 2 | | Total: | 4 | 4.04% |
| Total: | 19 | 14.50% | **Total:** | 99 | 100% |
| **Total:** | 131 | 100% | | | |
| **In adult aged 15–59 years** | | | **In adult aged 60+ years** | | |
| **Violence and accidents** | | | **Violence and accidents** | | |
| Buried alive or left behind | 2 | | Buried alive or left behind | 3 | |
| Club fight | 6 | | Club fight | 2 | |
| Homicide, killed by ache | 3 | | Shot by Paraguayan | 4 | |
| Shot/captured by Paraguayan | 47 | | Eaten by jaguar | 1 | |
| Snakebite or eaten by jaguar | 23 | | Snakebite | 3 | |
| Hit by lightning | 3 | | Lost | 3 | |
| Fell from tree/hit by falling tree | 2 | | Total: | 16 | 59.26% |
| Lost | 1 | | **Other causes** | | |
| Total: | 87 | 69.05% | Diarrhea | 3 | |
| **Infections/intoxications** | | | Sick (unspecified) | 2 | |
| Fever after eating pichu or kracho larvae/honey/palm starch or corn | 21 | | Old age | 6 | |
| Malaria | 2 | | Total: | 11 | 40.74% |
| Fever after touching blood | 3 | | **Total:** | 27 | 100% |
| Skin infection/sores on neck | 2 | | | | |
| Swollen body/systemic infection | 3 | | | | |
| Total: | 31 | 24.60% | | | |
| **Other causes** | | | | | |
| Childbirth | 3 | | **Overall number of deaths** | | |
| Stomach/liver problems | 2 | | Age 0–3 years | 131 | 34.20% |
| Sick in lungs or unspecified | 2 | | Age 4–14 years | 99 | 25.85% |
| Old age | 1 | | Age 15–59 years | 126 | 32.90% |
| Total: | 8 | 6.35% | Age 60+ years | 27 | 7.05% |
| **Total:** | 126 | 100% | Total: | 383 | 100% |

Data from Hill and Hurtado (1996)

**Aging Pathology, Table 2** Relations between some age-related dysfunctions and some "risk factors" or "protective drugs" (from (Libertini et al. 2018), simplified)

| Age-related dysfunctions | Cell turnover of the specific cells | Effect on the risk by: | | | | | | | Protective effect by: | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Ages | Diabete | Obesity/dyslipidemia | Hypertension | Smoke | Alcohol moderate use | Alcohol abuse | Statins | ACE-i, sartans |
| Endothelial dysfunction | Yes | + | + | + | + | + | − | + | + | + |
| Olfactory dysfunction | Yes | + | + | + | + | + | . | + | + | . |
| Age-related macular degeneration | No | + | + | + | + | + | −/ | + | ? | −? |
| Alzheimer's disease | No | + | + | + | + | + | − | + | + | + |
| Parkinson's disease | No | + | + | + | +/ | − | − | + | + | + |
| Hearing impairment | No | + | + | + | + | + | − | + | + | + |
| Emphysema and related diseases | Yes | + | + | − | + | + | − | + | + | + |
| Skin atrophy | Yes | + | + | . | . | . | . | . | + | + |
| Osteoporosis | Yes | + | + | + | + | + | − | + | + | + |
| Atrophy of other sensory neuronal cells with turnover | Yes | + | + | . | . | + | . | + | . | . |
| Cataract | Yes | + | + | + | + | + | − | + | +? | + |
| Testicular atrophy | Yes | + | + | + | . | + | / | + | . | / |
| Muscle atrophy | Yes | + | + | + | . | + | . | + | − | + |
| Cardiac insufficiency and related diseases | Yes | + | + | + | + | + | − | + | + | + |
| Diabetes and impairment of glucose tolerance | Yes | + | | + | + | + | − | + | −/ | + |
| Hepatic atrophy and related diseases | Yes | + | + | + | . | + | . | + | −/ | + |
| Renal insufficiency | Yes | + | + | + | + | + | − | + | + | + |
| Atrophy of oral mucosa and salivary glands | Yes | + | + | . | +? | + | . | + | . | . |
| Alopecia | Yes | + | + | + | + | + | +? | + | . | . |

Notes: +, risk or protective effect increased; −, risk or protective effect decreased; /, risk or protective effect unaltered; ?, doubtful results;., no specific study

With regard to the possible interpretation of the results reported in Table 2 as a test to evaluate the validity of nonadaptive and adaptive aging paradigms, it should be noted that both opposing theses could declare the results compatible with the respective thesis (Libertini et al. In press). In fact, a supporter of the nonadaptive aging paradigm could argue that the harmful general actions proposed as causes of aging if associated with other harmful factors could well explain the worsening of aging. Also, a supporter of the opposing thesis, the adaptive aging paradigm, could argue that the theory presupposes the existence of general mechanisms of aging that are altered by harmful factors with multiple but analogous deleterious effects on all the manifestations of aging. In both interpretations, particular types of drugs might have a general restraining action on the effects of the harmful factors.

However, a possible interpretation of the mechanisms underlying these relationships consistent with the adaptive aging paradigm was presented in more details in other works (Libertini 2014; Libertini et al. In press). Here, it will be expounded in short. The dysfunction of the endothelial cells served as a model to explain all the other alterations. The correct functionality of the endothelial cells, which are subject to turnover, is essential to avoid dangerous alterations of the vascular walls, namely, atherosclerosis and the

resulting diseases. Endothelial cell turnover is allowed by the replication of particular stem cells originating from the bone marrow, endothelial progenitor cells (EPCs). The number of EPCs decreases with age and also appears reduced by the so-called cardiovascular "risk factors" (e.g., hypercholesterolemia, diabetes, hypertension, cigarette smoking), while it is increased by some type of drugs (e.g., statins) (Hill et al. 2003), which could be defined as "protective factors." EPC reduction causes the slowing down of endothelial cell turnover, and this increases the danger of endothelial dysfunction and of the diseases that derive from alterations of the blood flow (e.g., cardiac infarctions, cerebral ischemia, peripheral ischemias). Moreover, with negative relation, the number of EPCs and the famous Framingham risk score (Wilson et al. 1987) turned out to be predictors of cardiovascular risk of equal value (Hill et al. 2003; Werner et al. 2005).

In the senile age, the reduction in EPC number, even in the absence of risk factors, increases the probability of cardiovascular diseases. The inverse relation between EPC number and risk factors could be explained on the basis of a pathological acceleration of endothelial cell turnover with consequent exhaustion of the EPCs that would be reduced or balanced by protective the factors. According to the adaptive aging paradigm, and using endothelial cells as a model, it was proposed the explanation of the dysfunctions reported in Table 2 and of the relationships with "risk factors" and "protective drugs." Regarding cells without cell turnover, the explanation appeals to the fact that perennial cells need for their function and vitality of satellite cells that are subject to turnover (Libertini and Ferrara 2016a; Libertini et al. In press).

## Aging Syndromes Caused by Genetic Alterations

Progeroid syndromes (PSs) are rare diseases, which are caused by harmful genetic mutations and show alterations that are similar to those of physiological aging. The term PS is not a synonym of progeria, which indicates a specific type of progeroid syndrome (Hutchinson-Gilford progeria syndrome). In general, these syndromes are caused by mutations of a single gene in DNA repair proteins: (i) nucleotide excision repair proteins, (ii) RecQ protein-like helicases, and (iii) nuclear envelope proteins (lamin A/C or LMNA) (Navarro et al. 2004). Each type of PS may be caused by various types of mutations affecting DNA repair proteins, and the clinical expressions may be variable (Navarro et al. 2004).

PSs are commonly described as "segmental aging syndromes" (Martin and Oshima 2000, p. 263), as they mimic multiple aspects but not all the characteristics of the physiological aging. For some of these syndromes (Werner syndrome, Hutchinson-Gilford progeria, Dyskeratosis congenita), there are clear similarities with physiological aging. On the contrary, for other syndromes (Bloom's syndrome, Cockayne syndrome, restrictive dermopathy, Rothmund-Thomson syndrome, Trichothiodystrophy, Wiedemann-Rautenstrauch syndrome, xeroderma pigmentosum), the analogies are limited to some characteristics of aging.

Some diseases, such as familial Alzheimer's disease and familial Parkinson's disease, manifest only precocious disorders of the nervous system that are also frequent in older individuals, and so they have been defined as "unimodal progeroid syndromes" (Martin and Oshima 2000, p. 263; Martin 2005, p. 523). Hypothetical PSs that seriously and precociously affect all organs and tissues are probably incompatible with life at an early age.

PSs (see Table 3), although rare, are of great interest for the study of aging, but, here, a detailed exposition and discussion of the various syndromes would be too long and complex.

However, a brief discussion of some features of two syndromes, Werner's syndrome (Martin and Oshima 2000) and dyskeratosis congenita (Dokal 2000), may be particularly interesting as they allow a better understanding of the general mechanisms that cause the different manifestations of these syndromes in the light of well-known aging-related phenomena (Marciniak and Guarente 2001).

In the context of the adaptive aging paradigm, the telomere theory explains aging as the effect of

**Aging Pathology, Table 3** Progeroid syndromes

| Name | Genetic transmission | Gene(s) affected | References |
|---|---|---|---|
| Bloom's syndrome (congenital telangiectatic erythema) | Autosomal recessive | RecQ helicase | Cunniff et al. (2017) |
| Cockayne syndrome | Autosomal recessive | Nucleotide excision repair proteins | Laugel (2013) |
| Dyskeratosis congenita | X-linked and autosomal recessive and dominant forms | Alterations of DKC1 gene or of the RNA part of telomerase | Dokal (2000); Vulliamy et al. (2001) |
| Hutchinson-Gilford progeria syndrome | Autosomal dominant | LMNA gene | Ullrich and Gordon (2015) |
| Restrictive dermopathy (tight skin contracture syndrome) | Autosomal recessive | LMNA gene | Navarro et al. (2004) |
| Rothmund-Thomson syndrome | Autosomal recessive | RecQL4 helicase gene | Larizza et al. (2010) |
| Trichothiodystrophy | Autosomal recessive | DNA repair genes | Faghri et al. (2008) |
| Werner syndrome | Autosomal recessive | DNA repair genes | Martin and Oshima (2000) |
| Wiedemann-Rautenstrauch syndrome | Autosomal recessive | DNA repair genes? | Arboleda et al. (2007) |
| Xeroderma pigmentosum | Autosomal recessive | DNA repair genes | Lehmann et al. (2011) |

the progressive decline in cell turnover of all cell types (Fossel 2004; Libertini 2006, 2009b), which is caused by telomere-telomerase system (Fossel's cell senescence "limited model" (Fossel 2004, p. 45)) and, in all tissues and organs, determines a progressive "atrophic syndrome" (Libertini 2009b, p. 95) characterized by:

> (a) reduced mean cell duplication capacity and slackened cell turnover;
> (b) reduced number of cells (atrophy);
> (c) substitution of missing specific cells with non-specific cells;
> (d) hypertrophy of the remaining specific cells;
> (e) altered functions of cells with shortened telomeres or definitively in noncycling state;
> (f) alterations of the surrounding milieu and of the cells depending from the functionality of the senescent or missing cells;
> (g) vulnerability to cancer because of dysfunctional telomere-induced instability ... (Libertini 2014, p. 1006)

About the point (g), see (DePinho 2000).

Cell turnover rates vary greatly depending on cell types (Richardson et al. 2014). On the one hand, we have cells such as those that allow a cell turnover of intestinal epithelium in about 3 to 6 days (Alberts et al. 2013).

In stem cells that allow a fast turnover, telomerase, whose activity is essential for cell turnover, is not very repressed. A model of alteration of cell turnover due to telomerase dysfunction is offered by dyskeratosis congenita. This syndrome occurs mainly in two forms: (i) autosomal, where there are defects in the gene encoding the RNA part of telomerase (Vulliamy et al. 2001), and (ii) X-linked, where the alteration of protein dyskerin compromises the RNA part of telomerase too (Mitchell et al. 1999). In both forms, there is low and inadequate telomerase activity and shorter than normal telomeres. The effects of telomerase deficiency can be observed in cell types with high turnover: "Problems tend to occur in tissues in which cells multiply rapidly – skin, nails, hair, gut and bone marrow – with death usually occurring as a result of bone-marrow failure" (Marciniak and Guarente 2001, p. 370). This explains well the clinical characteristics of dyskeratosis congenita, in particular bone marrow

failure, nail dystrophy, alopecia, leukoplakia, abnormal skin pigmentation, and gut disorders (Dokal 2000; Marciniak and Guarente 2001). Another feature of dyskeratosis congenita, consistent with the description of the "atrophic syndrome," point (g), is a higher rate of cancer that is likewise explained by the lack of telomerase and the consequent erosion of telomeres, which causes chromosomal instability (Marciniak and Guarente 2001).

This is another argument that contradicts the hypothesis explaining the restrictions of telomerase activity and therefore of cell turnover as a general defense against cancer in a terrible trade-off between aging and cancer restriction (Campisi 2000). This hypothesis was formulated to provide a necessary evolutionary explanation for mechanisms that progressively reduce fitness and which appear incompatible with nonadaptive aging paradigm. However, the hypothesis appears untenable for various reasons (Libertini 2009b; Mitteldorf 2013; Libertini and Ferrara 2016a).

Unlike cell types with rapid turnover, "some tissues that have the capacity for cellular replacement, but do not undergo continuous cell turnover, do not express telomerase in their progenitors. It is these tissues – such as the deep layers of the skin or the lining of the blood vessels – that might be expected to suffer most from age-associated telomere depletion, as they have no ability to regenerate telomeres. These tissues would also be greatly affected by defects in other pathways that maintain telomeres, such as DNA-recombination processes" (Marciniak and Guarente 2001, p. 371).

In Werner syndrome, there is the dysfunction of a helicase of the RecQ family that causes high somatic mutation rates (Fukuchi et al. 1989), a reduced replication capacity (Martin et al. 1970), and a dysfunction of somatic cells in the cycling state (Yu et al. 1996). In this syndrome, there is an atrophic syndrome for non-high turnover cells, and tissues composed of cells with slow turnover show specific alterations (e.g., lens epithelial cells- > cataracts, endothelial cells - > atherosclerosis, osteocytes - > osteoporosis, Langerhans β-cells - > type-2 diabetes, various types of derma cells - > skin atrophy and regional atrophy of subcutaneous tissue) (Martin and Oshima 2000).

## Conclusion

Accepting the thesis that aging is an adaptive and genetically programmed phenomenon, the troubles shown by the elderly fall into the following categories:

1. Diseases present both in older age and at any age, although in the elderly they may have greater severity in relation to the greater vulnerability of the organism.
2. Diseases caused by unhealthy substances or habits to which the species is not evolutionarily adapted. Such diseases can have a frequency or a gravity that is age-related, but they are not typical aging manifestations.
3. Diseases caused by genetic defects that cause manifestations that are identical, analogous, or related to those of normal aging.
4. Physiological aging, i.e., typical manifestations of aging, which cannot be defined as diseases because they are the physiological normality (unless one wants to define as disease also any physiological manifestation that causes suffering or alterations of a function).
5. Early and/or accentuated expression of aging manifestations as a consequence of unhealthy substances or habits.

This classification of the troubles in the elderly allows a rational approach for their prevention and treatment. However, for physiological aging, terms such as prevention and treatment are inappropriate, since a physiological phenomenon cannot be prevented or cured, but it is also possible to envisage and implement modifications of these manifestations by various types of actions (Libertini and Ferrara 2016b).

## Cross-References

▶ Aging and Cancer
▶ Aging Definition

- Aging for Perennial Cells
- Aging Mechanisms
- Anti-aging Strategies
- Dyskeratosis Congenita
- Human Aging and Metabolism
- Hutchinson-Gilford Progeria Syndrome
- Senolytic Drugs
- Timeline of Aging Research
- Werner Syndrome


## References


Alberts B, Bray D, Hopkin K et al (eds) (2013) Essential cell biology, 4th edn. Garland Science, New York

Arboleda G, Ramírez N, Arboleda H (2007) The neonatal progeroid syndrome (Wiedemann-Rautenstrauch): a model for the study of human aging? Exp Gerontol 42 (10):939–943. https://doi.org/10.1016/j.exger.2007.07.004

Campisi J (2000) Cancer, aging and cellular senescence. In Vivo 14:183–188

Cunniff C, Bassetti JA, Ellis NA (2017) Bloom's syndrome: clinical Spectrum, molecular pathogenesis, and cancer predisposition. Mol Syndromol 8(1):4–23. https://doi.org/10.1159/000452082

DePinho RA (2000) The age of cancer. Nature 408:248–254. https://doi.org/10.1038/35041694

Dokal I (2000) Dyskeratosis congenita in all its forms. Br J Haematol 110:768–779. https://doi.org/10.1046/j.1365-2141.2000.02109.x

Eaton SB, Shostak M, Konner M (1988) The Paleolithic prescription: a program of diet and exercise and a design for living. Harper and Row, New York

Faghri S, Tamura D, Kraemer KH, Digiovanna JJ (2008) Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. J Med Genet 45(10):609–621. https://doi.org/10.1136/jmg.2008.058743

Fossel MB (2004) Cells, aging and human disease. Oxford University Press, Oxford

Fukuchi K, Martin GM, RJJr M (1989) Mutator phenotype of Werner syndrome is characterized by extensive deletions. Proc Natl Acad Sci U S A 86:5893–5897. https://doi.org/10.1073/pnas.86.15.5893. [Published erratum appears in Proc Natl Acad Sci USA 86:7994 (1989)]

Hill K, Hurtado AM (1996) Ache life history. Aldine De Gruyter, New York

Hill JM, Zalos G, Halcox JPJ et al (2003) Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 348:593–600. https://doi.org/10.1056/NEJMoa022287

Larizza L, Roversi G, Volpi L (2010) Rothmund-Thomson syndrome. Orphanet J Rare Dis 29(5):2. https://doi.org/10.1186/1750-1172-5-2

Laugel V (2013) Cockayne syndrome: the expanding clinical and mutational spectrum. Mech Ageing Dev 134 (5–6):161–170. https://doi.org/10.1016/j.mad.2013.02.006

Lehmann AR, McGibbon D, Stefanini M (2011) Xeroderma pigmentosum. Orphanet J Rare Dis 6:70. https://doi.org/10.1186/1750-1172-6-70

Libertini G (2006) Evolutionary explanations of the "actuarial senescence in the wild" and of the "state of senility". ScientificWorldJournal 6:1086–1108. https://doi.org/10.1100/tsw.2006.209

Libertini G (2009a) Prospects of a longer life span beyond the beneficial effects of a healthy lifestyle. In: Bentely JV, Keller MA (eds) Handbook on longevity genetics, diet and disease. Nova Science Publisher, New York, pp 35–95

Libertini G (2009b) The role of telomere-telomerase system in age-related fitness decline, a tameable process. In: Mancini L (ed) Telomeres: function, shortening and lengthening. Nova Science Publ, New York, pp 77–132

Libertini G (2013) Evidence for aging theories from the study of a hunter-gatherer people (Ache of Paraguay). Biochem Mosc 78:1023–1032. https://doi.org/10.1134/S0006297913090083

Libertini G (2014) Programmed aging paradigm: how we get old. Biochem Mosc 79(10):1004–1016. https://doi.org/10.1134/S0006297914100034

Libertini G (2015) Non-programmed versus programmed aging paradigm. Curr Aging Sci 8(1):56–68

Libertini G (2017) The feasibility and necessity of a revolution in geriatric medicine. OBM Geriatrics 1(2). https://doi.org/10.21926/obm.geriat.1702002

Libertini G, Ferrara N (2016a) Aging of perennial cells and organ parts according to the programmed aging paradigm. Age (Dordr) 38(2):35. https://doi.org/10.1007/s11357-016-9895-0

Libertini G, Ferrara N (2016b) Possible interventions to modify aging. Biochem Mosc 81:1413–1428. https://doi.org/10.1134/S0006297916120038

Libertini G, Corbi G, Cellurale M, Ferrara N (In press) Age-related dysfunctions: evidence and relationship with some risk factors and protective drugs. A systematic review, Biochem. (Mosc.) 84(12)

Marciniak R, Guarente L (2001) Human genetics. Testing telomerase. Nature 413:370–372. https://doi.org/10.1038/35096663

Martin GM (2005) Genetic modulation of senescent phenotypes in Homo sapiens. Cell 120(4):523–532. https://doi.org/10.1016/j.cell.2005.01.031

Martin GM, Oshima J (2000) Lessons from human progeroid syndromes. Nature 408:263–266. https://doi.org/10.1038/35041705

Martin GM, Sprague CA, Epstein CJ (1970) Replicative life-span of cultivated human cells. Effects of donor's age, tissue, and genotype. Lab Investig 23:86–92

Mitchell JR, Wood E, Collins K (1999) A telomerase component is defective in the human disease dyskeratosis congenita. Nature 402:551–555. https://doi.org/10.1038/990141

Mitteldorf J (2013) Telomere biology: cancer firewall or aging clock? Biochem Mosc 78:1054–1060. https://doi.org/10.1134/S0006297913090125

Navarro C, De Sandre-Giovannoli A, Bernadr R et al (2004) Lamin A and ZMPSTE 24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. Hum Mol Genet 13:2493–2503. https://doi.org/10.1093/hmg/ddh265

Richardson RB, Allan DS, Le Y (2014) Greater organ involution in highly proliferative tissues associated with the early onset and acceleration of ageing in humans. Exp Gerontol 55:80–91. https://doi.org/10.1016/j.exger.2014.03.015

Ullrich NJ, Gordon LB (2015) Hutchinson-Gilford progeria syndrome. Handb Clin Neurol 132:249–264. https://doi.org/10.1016/B978-0-444-62702-5.00018-4

Vulliamy T, Marrone A, Goldman F et al (2001) The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature 413:432–435. https://doi.org/10.1038/35096585

Werner N, Kosiol S, Schiegl T et al (2005) Circulating endothelial progenitor cells and cardiovascular outcomes. N Engl J Med 353:999–1007. https://doi.org/10.1056/NEJMoa043814

WHO, ICD-10 (2016) http://www.who.int/classifications/apps/icd/icd10online/

WHO, ICD-11 (2018) https://icd.who.int/browse11/l-m/en

Wikipedia, World Ranking Total Deaths (2017), data from various sources, http://www.worldlifeexpectancy.com/world-rankings-total-deaths. See also: http://www.worldlifeexpectancy.com/sitemap

Wilson PW, Castelli WP, Kannel WB (1987) Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol 59:91–94G. https://doi.org/10.1016/0002-9149(87)90165-2

Yu CE, Oshima J, Fu YH et al (1996) Positional cloning of the Werner's syndrome gene. Science 272:258–262. https://doi.org/10.1126/science.272.5259.258