
5 Programmed Aging Paradigm and Aging of Perennial Neurons

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INTRODUCTION

THE PROBLEM

Alzheimer’s disease (AD), Parkinson’s disease (PD), and age-related macular degeneration (AMD) are degenerative diseases of the nervous system that manifest in the accumulation of specific substances (β -amyloid and tau protein for AD, α -synuclein for PD, A2E for AMD) and progressive impairment of psychomotor (AD, PD) or visual (AMD) functions (Weiner and Lipton 2009, Holz et al. 2013, Lim 2013, Pahwa and Lyons 2013, Husain and Schott 2016).

These diseases primarily affect elderly people and, as a result of the increase in life expectancy, there is a proportionate increase in the percentage and number of affected people. In the United States, approximately 96% of the 5.3 million Americans suffering from AD are over 65 years of age (Alzheimer’s Association 2015). The worldwide absolute number of people with dementia and over 65 years old was estimated or predicted at 24.3 million in 2001, 42.3 in 2020, and 81.1 in 2040 (Rizzi et al. 2014). AD frequency increases progressively with age so that the frequency is 1.5% at the age of 65, which becomes 30% at 80 (Gorelick 2004), leaving a very high probability that a centenarian will suffer from AD.

Excluding AD, PD is the most frequent of the neurodegenerative disorders (de Lau and Breteler 2006, Yao et al. 2013). In industrialized countries, its frequency is approximately 0.3% of the whole population, 1% of the population older than 60, and 4% of the individuals older than 80 (de Lau and Breteler 2006). The mean age of onset is around 60; however, PD manifestations begin before 50 years of age in 5%–10% of cases (Samii et al. 2004). “Meta-analysis of the worldwide data showed a rising prevalence of PD with age (all per 100,000): 41 in 40 to 49 years; 107 in 50 to

59 years; 173 in 55 to 64 years; 428 in 60 to 69 years; 425 in 65 to 74 years; 1087 in 70 to 79 years; and 1903 in older than age 80” (Pringsheim et al. 2014).

The estimated frequency of AMD is 1.4% at 70 years of age, 5.6% at age 80, and 20% at age 90 (Rudnicka et al. 2012), which implies that a centenarian is a probable AMD sufferer. The projected number of AMD patients in 2020 is 196 million, increasing to 288 million in 2040 (Wong et al. 2014).

In general, there are only symptomatic or palliative cures for these illnesses that do not appear able to block their basic pathogenetic mechanisms:

1. AD is treated by cholinesterase inhibitors (donepezil, galantamine, rivastigmine), memantine, souvenaid (Waite 2015), psychotropic drugs, etc., which aim to relieve its neurological and psychiatric manifestations, and by anti-amyloid or anti-tau drugs, which try to limit the accumulation of the substances that are considered to cause the disease. However, “Current therapies for Alzheimer’s disease do not modify the course of disease and are not universally beneficial” (Waite 2015).
2. PD is treated by pharmacotherapy, functional stereotaxic neurosurgery, physiotherapy, etc., all symptomatic cures, but “All treatments available until 2016 are of symptomatic nature. No therapy is currently available that slows down the progression of PD or even to prevent its manifestation” (Oertel and Schulz 2016).
3. There is no approved therapy for the atrophic (dry) form of AMD, while the costly treatment with anti-vascular endothelial growth factors (anti-VEGFs) contrast effectively the rapid evolution of the neovascular (wet) form (Azad et al. 2007, Nowak 2014), but do not block or revert it.

For the growing number of people affected and for the impairments caused by these diseases, the human, social, and economic costs are progressively growing and becoming unsustainable, especially for the cases of dementia. In the United States: “Total payments in 2015 for health care, long-term care and hospice services for people age 65 years with dementia are expected to be \$226 billion” (Alzheimer’s Association 2015).

In general, these diseases are described as without a known cause or origin, although many details of their pathogenetic mechanisms have been elucidated. AMD is defined as a “retinal disease with an unprecise etiopathogenesis” (Nowak 2014). PD “is a chronic, progressive neurological disease... The molecular mechanisms underlying the loss of these neurons still remain elusive” (Blesa et al. 2015). For AD: “The etiological mechanisms underlying these neuropathological changes remain unclear, but are probably caused by both environmental and genetic factors” (Reitz and Mayeux 2014).

These data indicate the gravity of the problem and the absence of an effective strategy to prevent and treat these illnesses. This serious and disastrous situation is a strong incentive to seek a completely new approach that could enable the understanding of the etiology of these diseases in order to develop and implement effective measures of prevention and treatment. In this work, a different interpretation of these illnesses is discussed to obtain a necessary premise for the achievement of such an ambitious and seemingly unrealistic goal.

NON-PROGRAMMED AND PROGRAMMED AGING PARADIGM

AD, PD, AMD, and other age-related illnesses of the nervous system (presbycusis, age-related hyposmia, and age-related deficits of other sensory abilities), disregarding the early cases due to “risk factors” (see below for the definition) or to genetic defects, are diseases whose frequency and severity are clearly related to age. Therefore, it appears logical that the nature of their connections with aging must be clarified for their proper understanding (and vice versa a better understanding of their origins may lead to a better understanding of aging mechanisms).

Therefore, it is an imperative preliminary to understand what aging is and the relationship between the mechanisms of aging and the mechanisms underlying these diseases.

It is necessary to specify that

- A comprehensive discussion about aging is outside the scope of this work. Only a few main points will be outlined while the appropriate papers will be indicated for a more detailed exposition.
- The interpretation here will be reaffirmed that the nature and mechanisms of aging are different and in clear contrast with the contradictory ideas generally accepted as a coherent (!) explanation for aging. However, such a different interpretation allows a unified and consistent view of the aforesaid diseases. Moreover, it will clarify why the current therapeutic approaches fail and will allow the proposition of a rationale for the development of effective treatment.

A necessary premise is to state a definition of aging that is descriptive and not vitiated by a preconceived explanation of this phenomenon. Therefore, aging will be defined precisely, in a neutral descriptive way, as “increasing mortality [= decreasing fitness] with increasing chronological age in populations in the wild” (Libertini 1988). This phenomenon, which has been documented for 175 different animal species (Nussey et al. 2013), may be also more concisely defined as “actuarial senescence” in reference to animals studied “in the wild” (Holmes and Austad 1995).

Aging is explained in two general ways, which are completely different and mutually incompatible and so deserve the definition of opposite “paradigms” (Libertini 2015a) according to the meaning that was proposed by Kuhn (1962).

The first paradigm, which could be defined as the “non-programmed aging paradigm,” or briefly “old paradigm,” explains aging as the effect of many degenerative phenomena, insufficiently contrasted by natural selection, which inexorably and inevitably cause the accumulation of random damages over time, as proposed by mutation accumulation (Medawar 1952, Hamilton 1966), antagonistic pleiotropy (Williams 1957, Rose 1991), disposable soma (Kirkwood 1977, Kirkwood and Holliday 1979), and other theories (Libertini 2015b). According to this paradigm, in principle, we could slow down and fight aging manifestations by using appropriate drugs and measures without the possibility to stop or reverse them (Libertini 2015a).

The second paradigm, which could be defined as the “programmed aging paradigm,” or briefly “new paradigm,” interprets aging as a physiological phenomenon that:

- Is evolutionarily favored in terms of supra-individual natural selection (Libertini 2015a).
- Is a particular type of phenoptosis (Skulachev 1997, Libertini 2012), that is, “programmed death of an individual” (Skulachev 1999).
- Is the result of specific mechanisms that are genetically determined and regulated, and therefore, in principle, might be modified up to a complete control of aging (Libertini 2009a,b).
- Has its specific pathological forms (Libertini 2009a,b, 2014).
- Has its specific phylogeny (Libertini 2015b).

A discussion about the arguments and the evidence that support or contrast each of the two paradigms has been proposed in another study where arguments and evidence appear to be against the old paradigm and support the new paradigm (Libertini 2015a).

Although the old paradigm is still the prevalent idea (Kirkwood and Melov 2011), the new paradigm will be considered a working hypothesis for the aims of this work. Accepting the interpretation of the new paradigm as a working hypothesis will provide an easy and unifying interpretation of AD, PD, AMD, and other diseases, which may be profitable for the goal of the formulation of

appropriate therapies. By contrast, the current concepts based on the old paradigm have led to the current situation of an insufficient understanding of these diseases and of ineffective therapies. The reader will be able to judge whether this approach is more consistent and efficacious.

SHORT DESCRIPTION OF THE TELOMERE THEORY

The new paradigm absolutely requires the existence of specific mechanisms that determine a progressive fitness reduction. These mechanisms are documented by a long series of authoritative studies and can be summarized under the term “telomere theory,” which for the sake of brevity cannot be explained here in detail. Therefore, only a brief description will be provided here, referring to a more detailed description from additional references (Libertini 2009a, 2014, Libertini and Ferrara 2016a).

During every replication cycle, the DNA molecule requires the telomerase enzyme in order to complete the duplication of a repetitive nucleotide sequence at its terminal regions, the telomere. In cells where the telomerase is inactive or partially active, any duplication results in telomere shortening. Since the telomere is covered by a heterochromatin hood with a fixed length, the gradual telomere shortening causes the sliding of the hood on the adjacent part of the DNA molecule, the subtelomere, which so is progressively inhibited. This inhibition has two main effects:

1. The progressive alteration of the regulatory functions of the subtelomere that determines a progressive alteration of numberless cell functions, a phenomenon here defined as “gradual cell senescence” or just as “gradual senescence” (Fossel 2004, Libertini 2014, 2015b).
2. An increase in the probability of activation of a particular cell program, the cell senescence, which is characterized by the blockage of cell replicative capacities and by the alterations of gradual senescence to its maximum degree (Ben-Porath and Weinberg 2005). The activation of this program is a random function with a probability that grows in every cell with the shortening of the telomere (Blackburn 2000) and so is likely related to the progressive inhibition of the subtelomere (Libertini and Ferrara 2016a) (Figure 5.1).

It has to be highlighted that, in plain contrast with the tenets of the old paradigm, the aforesaid cell alterations are not caused by irreversible degenerative phenomena, as it has been well demonstrated by experiments in which telomerase reactivation determined the regression of all the

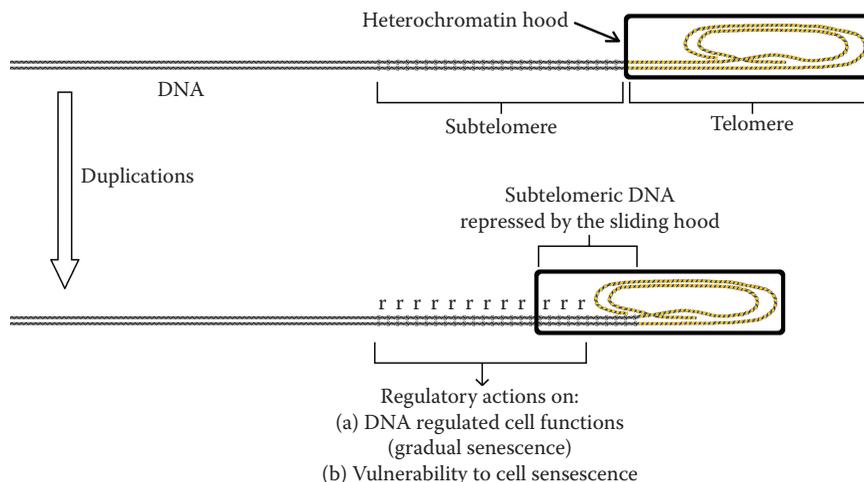


FIGURE 5.1 A scheme of the progressive subtelomere inhibition caused by the sliding of the telomeric hood. (Modified and redrawn from Figure 5.4 Libertini G. *Biochem. (Mosc.)* 2015b, 80(12):1529–46.)

aforesaid phenomena (Bodnar et al. 1998, Counter et al. 1998, Vaziri 1998, Vaziri and Benchimol 1998).

The majority of cell types in vertebrates undergo a continuous cell turnover. In a young individual, there is a perfect balance between the effects of various types of programmed cell death (apoptosis, keratinization of hair or epidermal cells, detachment of intestine cells, osteocytes phagocytized by osteoclasts, etc.) and the duplication of the opportune stem cells. As telomeres shorten, there is an increase in the number of cells in the cell senescence state, resulting in a gradual decrease in cell renewal capacity. This deficit, combined with the growing number of cells in various degrees of gradual senescence, leads to what has been defined as “atrophic syndrome” (Libertini 2009a), characterized by:

- “1. Reduced mean cell duplication capacity and slackened cell turnover
 2. Reduced number of cells (atrophy)
 3. Substitution of missing specific cells with nonspecific cells
 4. Hypertrophy of the remaining specific cells
 5. Altered functions of cells with shortened telomeres or definitively in a noncycling state
 6. Alterations of the surrounding milieu and of the cells depending on the functionality of the senescent or missing cells
 7. Vulnerability to cancer because of the dysfunctional telomere-induced instability ...”
- (Libertini 2014)

Factors such as unhealthy lifestyles (which cause diabetes mellitus, hypertension, obesity, etc.) and toxic substances (e.g., cigarette smoke and alcohol abuse), which may be defined on the whole as “risk factors,” increase cell duplication necessities and so accelerate the aging process. By contrast, factors such as healthy lifestyles and drugs that have organ protection qualities (“protective drugs”),

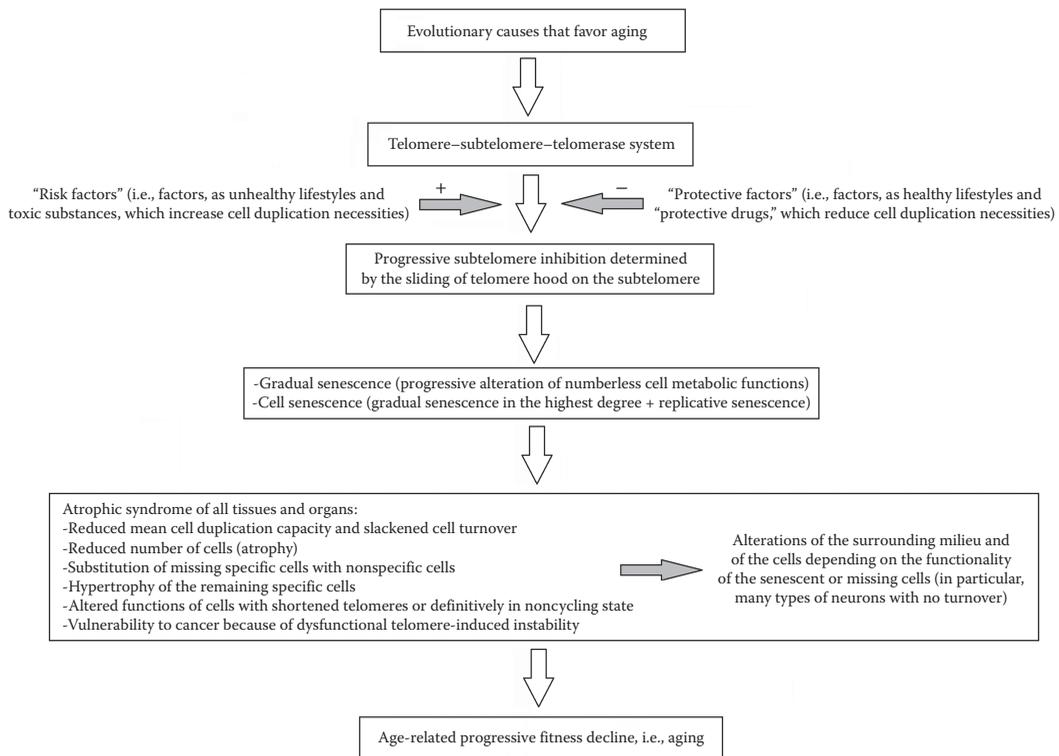


FIGURE 5.2 A scheme of the aging process. The discussion of the evolutionary causes is omitted in this work.

which may be defined on the whole as “protective factors,” reduce cell duplication capacities and neutralize the negative effects of the “risk factors” (Libertini 2009b) (Figure 5.2).

These mechanisms appear readily applicable to all cell types that are subject to cell turnover, and this could easily explain a large part of the aging phenomenon (Libertini 2009b). This, however, would not seem to relate to cells not subject to turnover, such as the majority of the neurons. However, a careful reading of the synthetic description of the atrophic syndrome shows (see point 6 in the description of the atrophic syndrome) that if a perennial cell is dependent for its functionality on other cells subject to turnover, the numerical and functional decline in these “satellite” cells may well explain the concomitant numerical and functional decline in the perennial cells (Libertini and Ferrara 2016b).

This discussion is deepened in the present analysis.

AGING OF NEURONS

TYPES OF NEURONS

There are many different neuronal cell types. For the purpose of this work, a preliminary distinction between two opposite extremes is necessary:

1. Certain types of specialized neurosensory neurons, such as olfactory receptor cells (ORCs), receive a signal from the external world by a single dendrite and are connected by a single axon to other neurons that process the signal (Bermingham-McDonogh and Reh 2011). For these neurons, the connections are quite simple and stereotyped and, in principle, the turnover of these cells should not entail any particular difficulty.
2. By contrast, each neuron in the central nervous system (CNS) is connected to a large number of other neurons. According to an estimate, in the human brain, there are 10^{11} neurons connected by 10^{14} synapses (Williams and Herrup 1988), that is, there is an estimated average of 1000 synapses for each neuron. Given the large number of synapses and the expected variability in the connections between neurons, the possible replacement of a neuron with a new neuron should also restore any previous connection through an unlikely mechanism that would be exceedingly complex. If brain functions are dependent on the net of synapses among neurons that have been established over time, and the connections are different for each individual neuron and, on the whole, are specific for each individual, the failure to restore the exact synapses would create unbearable harm caused by any turnover of these neurons. This would justify the absence of cell turnover for CNS neurons, with some exceptions (Horner and Gage 2000, Zhao et al. 2008), for example, “for certain forms of brain function involving the olfactory bulb and the hippocampus, which is important for some forms of learning and memory” (Zhao et al. 2008). This absence is likely for functions that require new connections and for which new neurons are not a problem but a necessity.

Different strategies are necessary for these two opposite neuronal cell types. For the first type, as will be expounded in more detail for the ORCs, the strategy of cell turnover can be implemented as well as it is implemented for nonneuronal cells.

For the second type of neuron, the practical impossibility of replacing the neurons without damaging brain functions and, at the same time, the need to ensure their cell functionality even after many years are solved, as we will see in the following sections, by a different strategy that is very well documented for a neuronal cell type, the retinal photoreceptor cells, and is quite likely for other types of CNS neurons.

For the following discussion, endothelial cells will be used as an important example of nonneuronal cells that undergo turnover. Risk factors for cardiovascular diseases, such as age, diabetes,

smoking, body mass index (i.e., overweight and obesity), and hypertension (Wilson et al. 1987), are associated with a reduced number of endothelial progenitor cells (Hill et al. 2003), likely caused by a quicker turnover of endothelial cells: “continuous endothelial damage or dysfunction leads to an eventual depletion or exhaustion of a presumed finite supply of endothelial progenitor cells ... continuous risk-factor-induced injury may lead to eventual depletion of circulating endothelial cells” (Hill et al. 2003). This would be analogous to what happens in patients with muscular dystrophy, where there is an exhaustion of skeletal muscle stem cells (Webster and Blau 1990, Decary et al. 2000, Seale et al. 2001) as well as in a number of age-related conditions (Tyner et al. 2002, Geiger and Van Zant 2002).

ACE inhibitors, AT1 blockers (sartans), and statins, which may be considered protective drugs for cardiovascular diseases, improve endothelial function (Su 2015). Statin therapy accelerates reendothelialization through endothelial progenitor cells (Walter et al. 2002), and this could explain the effects of statins, and likely of other “protective drugs,” on the prevention and treatment of cardiovascular diseases.

OLFACTORY RECEPTOR CELLS

ORCs are specialized neurons, which are present in the upper part of the nasal cavity and allow the perception of smell. They “have a single dendrite that extends to the apical surface of the epithelium and ends in a terminal knob, which has many small cilia extending into the mucosa. A single axon projects through the basal side of the epithelium through the lamina cribrosa to terminate in the olfactory bulb. Each of the receptor neurons expresses one of a family of over 1000 olfactory receptor proteins ... The neurons are surrounded by glial-like cells, called sustentacular cells. Other cells in the epithelium contribute to the continual production of the new receptor neurons ...” (Bermingham-McDonogh and Reh 2011) (Figure 5.3).

The continuous turnover of the ORCs in normal individuals is well documented (Maier et al. 2014). “The ongoing genesis of olfactory receptor cells is common to all vertebrates (see Graziadei and Monti Graziadei, 1978, for a review) and the rate of production is quite high. The production of new olfactory receptor cells is critical to the maintenance of this system, as the olfactory receptor cells only last a few months. The rate of production of new olfactory receptor cells is balanced by their loss so that a relatively stable population of these receptors is maintained” (Bermingham-McDonogh and Reh 2011).

Analyses of the healthy olfactory epithelium show that the turnover of ORCs is enabled by some slow cycling stem cells and by transit-amplifying progenitor cells (globose basal cells and horizontal basal cells, respectively) (Caggiano et al. 1994, Huard et al. 1998, Chen et al. 2004, Leung et al. 2007, Iwai et al. 2008). This two-stage modality of cell reproduction to allow cell turnover is similar to that of the epidermis and other cell types (Watt et al. 2006).

Owing to their position, ORCs are highly exposed to damage by external factors but have simple connections as each cell has a single dendrite, with many small ramifications in the mucosa, and a single axon. Therefore, the turnover of the ORCs is both necessary and simple. If this turnover follows the same patterns as other cell types, one can predict an age-related slowing of cell substitution with the consequent impairment of olfactory function. Other factors, perfectly compatible with the aforesaid mechanism, which could contribute to this progressive impairment, are: (i) an increase in the proportion of ORCs with various degrees of gradual senescence; (ii) age-related slowing of cell turnover of the gliocytes that are satellites of ORCs and of olfactory bulb neurons; and (iii) age-related decay of other CNS areas that contribute to olfactory function.

As a matter of fact, the impairment of olfactory function is age-related (Schubert et al. 2012, Doty and Kamath 2014, Gouveri et al. 2014), and approximately 50% of 65–80-year-old individuals suffer from clear olfactory dysfunction (Doty et al. 1984, Duffy et al. 1995, Murphy et al. 2002).

If AD, PD, AMD, and other diseases of the CNS are caused (as discussed below) by the failure in cell turnover of the gliocytes that are essential neuronal satellite cells, a clear relation between

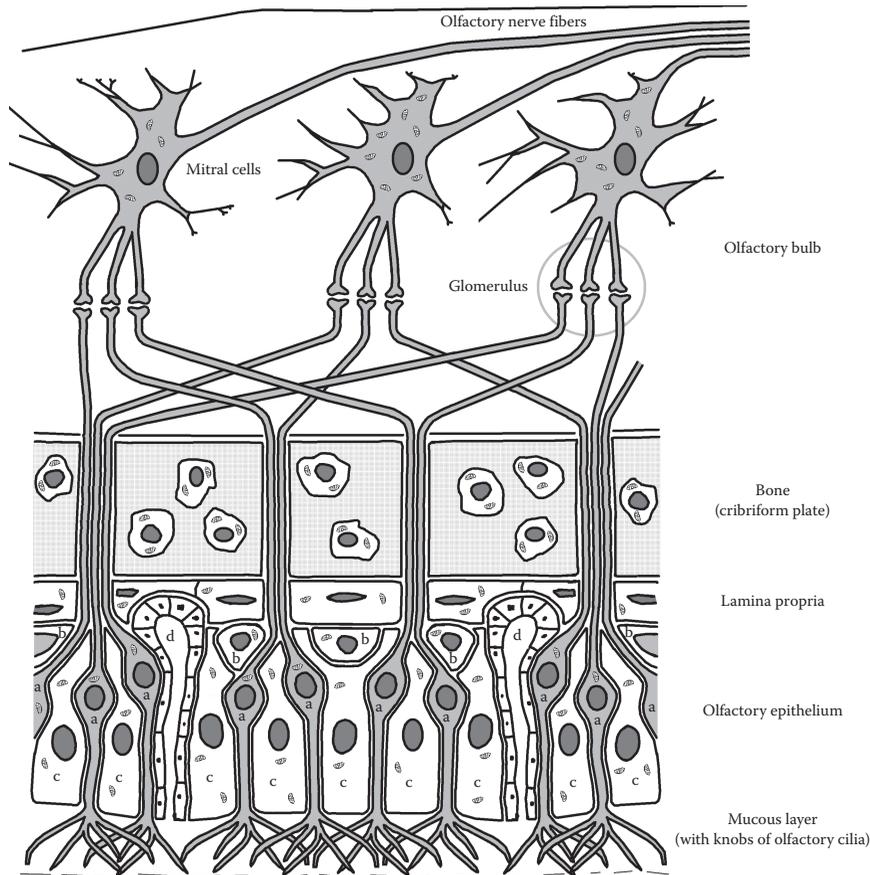


FIGURE 5.3 A scheme of the peripheral olfactory system. In the olfactory epithelium: a = olfactory receptor cells, b = regenerative basal cells; c = sustentacular or supporting cells (differentiated gliocytes); d = olfactory (Bowman's) glands.

olfactory dysfunction and these diseases is expected. In fact: (i) olfactory dysfunction has been estimated to be as high as 90% of early-stage PD cases (Doty 2012) and 100% in AD (Duff et al. 2002); (ii) hyposmia is a common symptom in PD dementia, in AD, and in other forms of dementias (Barresi et al. 2012); (iii) it has been reported as an early sign of PD and a precocious and constant characteristic of AD and of dementia with Lewy bodies (DLB) (Factor and Weiner 2008); and (iv) there is a correlation between olfactory dysfunction and AMD (Kar et al. 2015).

There is a possible association between olfactory dysfunction and unhealthy lifestyles: (i) "Olfactory dysfunction is a known complication of diabetes" (Mehdizadeh et al. 2015); (ii) there is an association between olfactory dysfunction and type 2 diabetes or hypertension (Gouveri et al. 2014); (iii) obesity is associated with the risk of olfactory dysfunction (Richardson et al. 2004, Patel et al. 2015); (iv) in the rat, ethanol and tobacco smoke damage olfactory function, and this "could explain the decreased olfactory ability seen in patients who use these products" (Vent et al. 2003); (v) "alcoholism appears to be associated with a variety of disturbances in olfactory processing" (Rupp et al. 2004); and (vi) prevention and treatment of such diseases indicated as risk factors should also be effective for the olfactory dysfunctions. It was not possible to find studies on the specific use of drugs for such purposes. However, in a mouse model, anosmia caused by a toxic substance was successfully treated by a statin (Kim et al. 2012).

Given that ORC turnover is essential and simple for the aforesaid reasons, the turnover of other sensory neurons and, consequently, an age-related functional decline may also be expected.

For example, in humans: (i) taste buds turn over rapidly, with an average life span of 8–12 days, and an age-related decline in function is documented (Feng et al. 2014); (ii) “Reported changes include reduced total number of taste buds, reduced taste bud density in the epithelium, and reduced number of taste cells per taste bud” (Feng et al. 2014); (iii) there is a decline in gustatory capacities of patients with AD (Aliani et al. 2013). A negative correlation between age and the number of Meissner’s corpuscles per mm² was observed (Iwasaki et al. 2003) and “there is an approximate two-thirds reduction in numbers of Pacinian and Meissner’s corpuscles with age” (Griffiths 1998).

RETINAL PHOTORECEPTORS

Retinal photoreceptors (cones and rods) are very specialized nervous cells and have complex connections with other neurons of the retina, where the initial processing of data perceived by the eye occurs. Therefore, photoreceptors belong to the aforesaid second type of neurons (as do almost all neurons) and have no turnover. However, photoreceptors depend on other cells with turnover, the cells of the so-called retinal pigment epithelium (RPE), which consist of specialized gliocytes that turn over. The heads of the photoreceptors are associated with RPE cells. Photoreceptors have particular membranes covered by photopsin molecules, which allow light reception but suffer from high oxidative damage, and each day about one-tenth of these membranes is phagocytized and metabolized by RPE cells. At the same time, photoreceptors synthesize an equal quantity of membrane so that cell structure and function remain stable. An RPE cell serves approximately 50 photoreceptors and, therefore, each day metabolizes the membranes of approximately five photoreceptors, showing

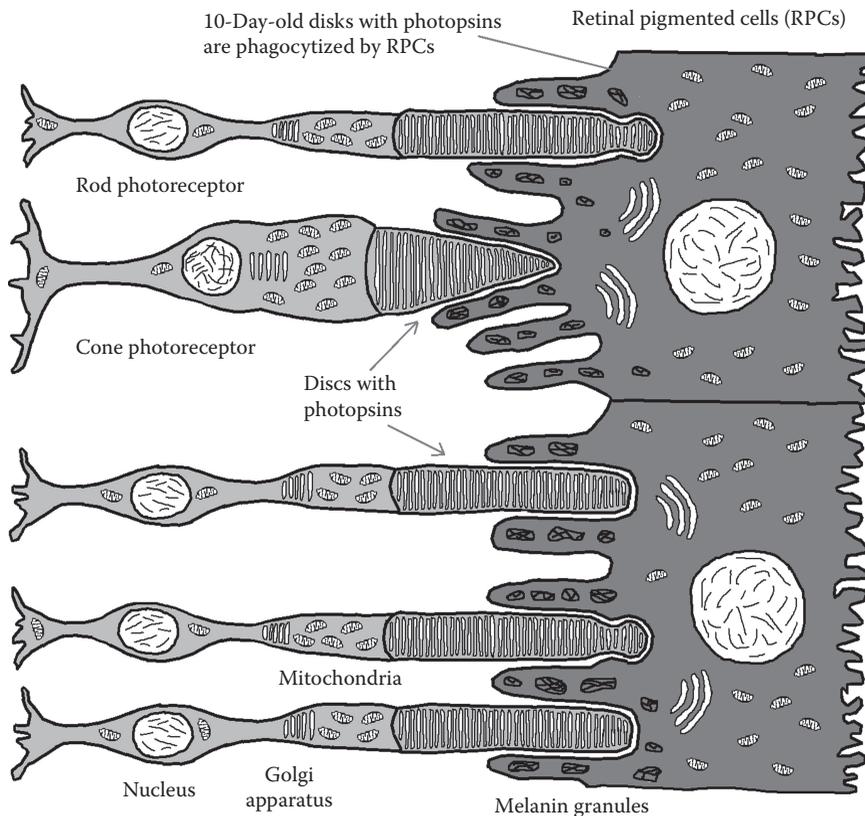


FIGURE 5.4 A scheme of some photoreceptor cells and retinal pigmented cells.

an exceptional metabolic activity. RPE function is essential for the vitality of the photoreceptors (Fine et al. 2000, Jager et al. 2008) (Figure 5.4).

The limits in the duplication capacities of RPE stem cells do not allow for an unlimited turnover of these cells. The age-related decline in RPE cell turnover determines the enlargement of the remaining RPE cells and the accumulation of A2E, a breakdown product derived from vitamin A, and of other damaging substances (Sparrow 2003). The continued decline in turnover causes the formation of holes in the RPE, and the photoreceptors die at this point (Berger et al. (1999)).

This decline is more precociously evident in the pivotal part of the retina, the macula, where photoreceptors are denser and A2E accumulation is most abundant (Sparrow 2003, Ablonczy et al. 2012). For this reason, the trouble is defined as “age-related macular degeneration,” although the entire retina is affected (Fine et al. 2000).

AMD may arise at precocious ages depending on the particular genetic defects affecting RPE cells or from the effects of toxic substances or metabolic stresses caused by unhealthy lifestyles. Disregarding these cases, the frequency of AMD increases exponentially with age (Rudnicka et al. 2012) and for its genesis and frequency, it should be considered a standard feature of aging.

Risk factors for cardiovascular diseases (Wilson et al. 1987) can have detrimental effects on RPE turnover that are analogous to those on endothelial progenitor cells (Hill et al. 2003), and this could justify their association with AMD (Klein et al. 2007) and between unhealthy lifestyles and AMD (Mares et al. 2011). “Smoking is the risk factor most consistently associated with AMD. Current smokers are exposed to a two to three times higher risk of AMD than non-smokers and the risk increases with intensity of smoking” (Armstrong and Mousavi 2015).

About the possible prevention or treatment of AMD by drugs, “... epidemiologic, genetic, and pathological evidence has shown AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD. ... Evidence from currently available randomized controlled trials is insufficient to conclude that statins have a role in preventing or delaying the onset or progression of AMD” (Gehlbach et al. 2015).

As regards alcohol consumption and the risk of vascular diseases, low alcohol consumption appears to have a beneficial effect (Roerecke and Rehm 2014, Gardner and Mouton 2015, de Gaetano et al. 2016). “On the other hand, ethanol chronically consumed in large amounts acts as a toxin to the heart and vasculature” (Gardner and Mouton 2015). “Evidence consistently suggests a J-shaped relationship between alcohol consumption ... and all-cause mortality, with lower risk for moderate alcohol consumers than for abstainers or heavy drinkers” (de Gaetano et al. 2016). For AMD: “Moderate alcohol consumption is unlikely to increase the risk of AMD” (Armstrong and Mousavi 2015). However, in the Beaver Dam Offspring Study, no association between a history of heavy drinking and early AMD was observed (Klein et al. 2010).

Since the retina is constantly exposed to light and has high oxygen content, it is clearly susceptible to strong oxidative damage. However, in evident contrast with the predictions of the old paradigm, antioxidant supplements did not prevent early AMD as shown by the results of the meta-analysis of 12 studies (Chong et al. 2007).

BRAIN NEURONS AND THE GENESIS OF AD

The preceding section has shown that specialized neurons without cell turnover (retina photoreceptors) depend for their function and vitality on specialized gliocytes with cell turnover (RPE cells). This suggests that other types of neurons without cell turnover (mostly CNS neurons) could also be dependent on specific gliocytes with cell turnover (Figure 5.5). Therefore, the gradual senescence and cell senescence of these specialized gliocytes may cause pathologies equivalent to AMD for their genesis.

Even without considering the proposed AMD genesis, AD was hypothesized to have originated from the functional decline in particular gliocytes caused by telomere shortening (Fossel 1996,

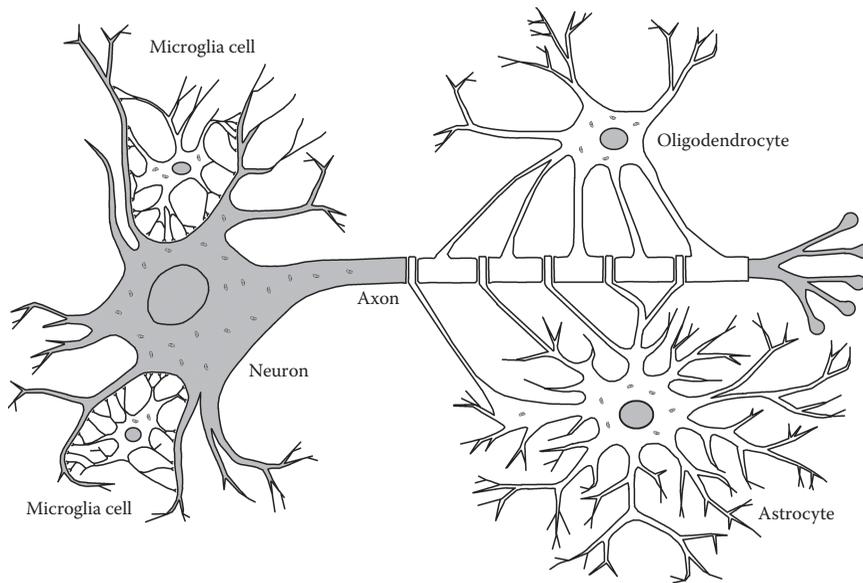


FIGURE 5.5 A scheme of a neuron and its auxiliary gliocytes.

2004): “One function of the microglia ... is degradation of β -amyloid through insulin-degrading enzyme (IDE), a function known to falter in Alzheimer disease ...” (Fossel 2004, p. 233).

The role of microglial cells in the degradation of β -amyloid protein is well known (Qiu et al. 1998, Vekrellis et al. 2000, Miners et al. 2008), as is the fact that this function is altered in AD (Bertram et al. 2000) with the consequent accumulation of the substance. As regards the relation between the decline in microglial function and telomere length, a significantly reduced telomere length in circulating monocytes is associated with at least vascular dementia (von Zglinicki et al. 2000).

The hypothesis that AD is determined by the decline in microglial cells was proposed again without mentioning the association between satellite gliocyte failure and AMD (Flanary 2009) or, with stronger arguments, considering it (Libertini 2009a, 2009b).

“A cell senescence model might explain Alzheimer dementia without primary vascular involvement” (Fossel 2004, p. 235) and it is likely that many AD cases have in part a vascular etiology caused by age-related endothelial dysfunction (Fossel 2004). The similarities or identities between the symptoms of a “pure” AD and those of a “pure” vascular dementia and the cases where the two conditions overlap to varying extents must not obscure an affinity that is deeper and not linked only to some identical symptoms.

If it is true that AD neuronal decay results from the decline in satellite cells and that vascular dementia is a neuronal decay caused by vascular dysfunction, there is a common pathogenetic mechanism in their origins. The vascular diseases, including those that affect the brain, are caused by endothelial dysfunction originating from the depletion of their turnover capacity marked by an insufficient number of endothelial progenitor cells (Hill et al. 2003). Similarly, AD could originate from microglial dysfunction caused by the slowing or exhaustion of microglia cell turnover capacity. In both cases, telomere shortening in the stem cells of the endothelial cells or of the microglial cells is the primary cause.

Therefore, the risk factors for cardiovascular diseases and for AD, in general, should both accelerate telomere failure, whereas protective factors should counter these effects. Moreover, risk factors for cardiovascular diseases and for AD should coincide, and analogously protective factors for the same diseases should coincide.

In support of these claims: (i) an association between cardiovascular risk factors and AD has been shown (Vogel et al. 2006, Rosendorff et al. 2007); (ii) cigarette smoking is a risk factor for AD (Durazzo et al. 2014); (iii) many reviews, with some exceptions (e.g., Li et al. 2016), maintain a positive correlation between diabetes mellitus and the risk of developing AD (Baglietto-Vargas et al. 2016, Rani et al. 2016, Saedi et al. 2016, Vicente Miranda et al. 2016); (iv) there is a positive relation between hypertension and AD risk (Qiu et al. 2005, Michel 2016); (v) statins, ACE inhibitors, and sartans, “protective drugs” for cardiovascular diseases, are considered effective against AD (Vogel et al. 2006, Ellul et al. 2007); and (vi) in a recent meta-analysis, ACE inhibitors and sartans appear to reduce the risk of developing AD (Yasar et al. 2016); (vii) “Mid-life dyslipidemia appears to play an important role in the development of AD amongst a host of other risk factors that affect vascular health. Results from observational cohorts have been mixed, though many of the highest-quality studies have found a protective effect for statins” (Wanamaker et al. 2015).

As regards alcohol consumption, “Light to moderate drink may decrease the risk of Alzheimer’s disease” (Ilomaki et al. 2015). A study has highlighted “weak evidence” for the association between a higher risk of AD and excessive alcohol consumption while “a lower risk of AD is associated with moderate alcohol consumption” (Campdelacreu 2014).

The traditional hypothesis that the decisive factor for AD pathogenesis is the damage accumulation of substances such as β -amyloid and tau protein has been widely contradicted by the failures of the pharmaceutical industry in the trials based on this thesis. Drugs or vaccines used with the aim to counter the formation of β -amyloid plaques have been disappointing, not for their ability to eliminate the plaques but for the purpose of obtaining positive clinical effects (Abbott 2008). In particular, in 2008, a study showed that an experimental amyloid peptide vaccine was very effective in eliminating the plaques or in avoiding their formation, but: “Seven of the eight immunised patients who underwent post-mortem assessment, including those with virtually complete plaque removal, had severe end stage dementia before death” (Holmes et al. 2008) and the authors observed “Although immunization with A β 42 resulted in clearance of amyloid plaques in patients with Alzheimer’s disease, this clearance did not prevent progressive neurodegeneration” (Holmes et al. 2008). A recent authoritative study (Sevigny et al. 2016) has used a human monoclonal antibody (aducanumab) to eliminate the amyloid- β plaques. The technique has shown significant and dose-dependent effectiveness in eliminating the plaques, while the clinical results (for which one must observe that the study was not specifically designed) remain uncertain. After 1 year of treatment, one of the two clinical evaluation parameters (Mini Mental State Examination) showed positive results for the doses of antibody 3 and 10 mg/kg, but for the intermediate dose of 6 mg/kg, the result was similar to that of placebo.

The hypothesis that AD originates from the accumulation of β -amyloid (amyloid cascade hypothesis) has been strongly criticized (Herrup 2010, Mondragón-Rodríguez et al. 2010, Reitz 2012), but there is a reluctance to drop it, perhaps for the false idea that there is no plausible alternative such as the one discussed in the current work.

N-Methyl-D-aspartate receptor antagonist (e.g., memantine), acetylcholinesterase inhibitors (e.g., galantamine, donepezil, tacrine, and rivastigmine), and other drugs are used to treat AD (Mendiola-Precoma et al. 2016). However, “The only drugs available for Alzheimer’s patients aim to treat symptoms ... They are marginally effective at best” (Abbott 2008). Moreover, the treatment of AD cognitive alterations by antipsychotic drugs increased the long-term risk of mortality (Ballard et al. 2009).

BRAIN NEURONS AND THE GENESIS OF PD

PD is characterized by the accumulation of the protein α -synuclein (AS) inside CNS neurons, which forms particular inclusions known as Lewy bodies (Davie 2008, Schulz-Schaeffer 2010). A disease that is akin to PD, classified as a Parkinson-plus syndrome, is the DLB (Nuytemans et al. 2010). It has the signs of a primary parkinsonism but shows some additional features (Samii et al. 2004). In addition, multiple system atrophy is a rare genetic disease in which AS accumulates in oligodendrocytes (Sturm and Stefanova 2014).

While AD is referred to as a tauopathy due to the accumulation of tau protein and the formation of neurofibrillary tangles, PD, DLB, and multiple system atrophy are referred to as synucleinopathies for the accumulation of AS (Galpern and Lang 2006). Despite the difference between the accumulated substances, many symptoms and pathological manifestations are similar or identical in these neuropathies (Aarsland et al. 2009).

PD is mainly a disease of the CNS motor system because its more common and typical symptoms include disorders of movement caused by extrapyramidal motor dysfunction. However, nonmotor manifestations such as dementia and sensory deficits are common (Barnett-Cowan et al. 2010). In PD cases without dementia, behavior and mood alterations (e.g., depression, anxiety, apathy, etc.) are more frequent than in the general population and are common symptoms in cases with dementia (Jankovic 2008).

Dementia is frequent in PD patients, in particular at advanced stages, and AD patients often manifest parkinsonism (Galpern and Lang 2006). In PD patients, the risk of dementia is two to six times that of the whole population and is related to disease duration (Caballol et al. 2007). However, for AD patients, dementia is more precocious and senile plaques and neurofibrillary tangles are characteristic of AD, while they are uncommon in PD without dementia (Dickson 2007).

As regards the distinction between the clinical manifestations of PD and DLB, “PD and DLB are common neurodegenerative diseases in the population over the age of 65. About 3% of the general population develops PD after the age of 65, whereas about 20% of all diagnosed dementia patients have DLB ... In both disorders movement and cognition, as well as mood and autonomic function are severely affected. Diagnosis to distinguish PD and DLB is very difficult, because of the overlap of symptoms and signs ...” (Brück et al. 2016).

In PD pathogenesis, Lewy bodies are found in the olfactory bulb, medulla oblongata and pontine tegmentum before clear symptoms appear. In the following phases, they are present in the substantia nigra, in some regions of the basal forebrain and of the midbrain, and finally in the neocortex (Davie 2008). PD motor symptoms are interpreted as a consequence of neuronal cell death in a particular area of the brain (the pars compacta region of the substantia nigra), which causes a reduction in dopamine secretion (Obeso et al. 2008).

In the aforesaid areas, there is neuronal degeneration and loss, for which Lewy bodies have been proposed not to be the cause of neuron death but as a protection against other factors (Obeso et al. 2010, Schulz-Schaeffer 2010). In demented AD patients, Lewy bodies are observed in particular in cortical areas in the brain, and it has been suggested that “reduced AS clearance is involved in the generation of AS inclusions in DLB and PD” (Brück et al. 2016), but this does not clarify if Lewy bodies are the cause of neuronal degeneration or a simple consequence of the cause.

About this, some evidence must be considered
“Glial cells are important in supporting neuronal survival, synaptic functions and local immunity ... However, glial cells might be crucial for the initiation and progression of different neurodegenerative diseases, including ASP [α -Synucleinopathies] ...” (Brück et al. 2016).

“... microglial cells contribute to the clearance of debris, dead cells and AS thereby supporting neuronal survival. But on the other hand, microglial cells can get over-activated in the course of the disease and might contribute to disease initiation and progression by enhancing neurodegeneration through elevated oxidative stress and inflammatory processes” (Brück et al. 2016).

In analogy with AMD and AD genesis, these elements suggest that the pivotal event in PD genesis is the loss of essential functions of specific gliocytes (astrocytes), mainly dedicated to axon trophism, and the activation of astroglial and microglial cells could be an event caused by the consequent AS accumulation (Morales et al. 2015), while the decline in function of these specific gliocytes would be caused by the decline in their turnover.

As regards the associations of PD with “risk factors,” there is the following evidence: (i) A study has shown that, in middle age, high skinfold thickness is associated with PD (Abbott et al. 2002); (ii) Metabolic syndrome (i.e., in short, an unhealthy lifestyle that causes dyslipidemia, obesity, glucose intolerance, hypertension, etc.) has been indicated as an important risk factor for PD (Zhang

and Tian 2014); (iii) Independently of other risk factors, body mass index appears to be related to an increased risk of PD (Hu et al. 2006), and obesity in midlife increases the risk of dementia (Whitmer et al. 2005); (iv) Hyperglycemia in aging subjects is associated with PD (Hu et al. 2007, Tomlinson and Gardiner 2008); (v) Type 2 diabetes is a risk factor for PD (Vicente Miranda et al. 2016); (vi) Alcohol (light to moderate) use has been found to have an inverse association with PD (Ishihara and Brayne 2005) while alcohol use disorder appears to increase the risk of PD (Eriksson et al. 2013).

The risk of PD appears to be lowered by statins (Gao et al. 2012, Friedman et al. 2013, Undela et al. 2013, Sheng et al. 2016). Captopril, an angiotensin-converting enzyme inhibitor, has been shown to protect nigrostriatal dopamine neurons in animal models for PD (Lopez-Real et al. 2005, Sonsalla et al. 2013). A strange finding is that cigarette smoking, a risk factor for AD (Durazzo et al. 2014), AMD (Klein et al. 2007), hearing loss (Fransen et al. 2008, Chang et al. 2016), and olfactory dysfunction (Vent et al. 2003), appears to lower PD risk (Li et al. 2015). A possible explanation is that nicotine has a neuroprotective effect on dopaminergic neurons and could even be used as a medicine to contrast PD progression or symptoms (Thiriez et al. 2011, Quik et al. 2015).

Hyperhomocysteinemia (HHcy), which is considered a risk factor for endothelial dysfunction and for vascular diseases (Woo et al. 1997), has been shown to be associated with AD and PD (Kruman et al. 2000). However, limiting the discussion to AD, “it is still controversial if HHcy is an AD risk factor or merely a biomarker” (Zhuo et al. 2011).

HEARING NEURONS

The organ of Corti is a sensory receptor inside the cochlea of the inner ear, which has a hearing function. It has differentiated neurons, the auditory or hair cells, divided into two groups (inner and outer hair cells) and connected to specific neurons (spiral ganglion neurons). In a newborn, for each organ of Corti, there are approximately 35,000 neurons and 15,500 hair cells, and both of these cell types are perennial (Wong and Ryan 2015): “... no epithelial maintenance has been described for

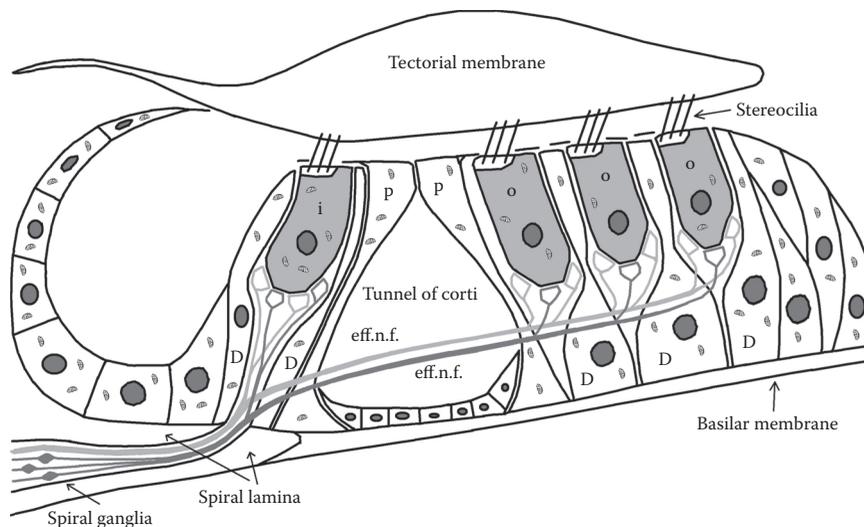


FIGURE 5.6 Organ of Corti. i = inner hair cells; o = outer hair cells; D = Deiters' cells; p = pillar cells; aff.n.f. = afferent nerve fibers of cochlear nerve; eff.n.f. = afferent nerve fibers of cochlear nerve. Hair cells, specialized neurons that constitute the sensorineural cells of the auditory organ, are supported by Deiters' cells, which are specialized gliocytes.

the hair cells of the cochlea of mammals, though hair cell addition and repair occur in lower vertebrates ...” (Maier et al. 2014) (Figure 5.6).

It is well known that there is an age-related progressive reduction of hearing ability (Zhan et al. 2010). In the United States, hearing loss of more than 25 dB in speech frequency pure tone average has been reported to be 45.6%, 67.6%, 78.2%, and 80.6% in groups aged 70–74, 75–79, 80–84, and >84 years, respectively (Lin et al. 2011b). Noise exposure is not an indispensable cause for the development of presbycusis, as it has been observed in healthy animals that were reared in silence (Sergeyenko et al. 2013, Yan et al. 2013).

Cardiovascular and cerebrovascular diseases, diabetes, and cigarette smoking have been associated with increased risk of hearing loss (Yamasoba et al. 2013). In a study with 3,753 participants, “current smokers were 1.69 times as likely to have a hearing loss as nonsmokers” (Cruikshanks et al. 1998) and in another study with 12,935 participants, “Current smoking was associated with hearing impairment in both speech-relevant frequency and high frequency across all ages” (Chang et al. 2016). Interestingly, “a remarkable parallelism between the risk factors for ARHI [age-related hearing impairment] and those for CVD [cardiovascular disease] with similar roles for smoking, high BMI, and regular moderate alcohol consumption” (Fransen et al. 2008) has been observed.

Cardiovascular risk factors “adversely affect hearing acuity” (Oron et al. 2014). Type 2 diabetes mellitus is associated with alterations in hearing (Akinpelu et al. 2014, Calvin and Watley 2015, Helzner and Contrera 2016), and hypertension has been found to be associated with cochlear hearing loss (Przewoźny et al. 2015). In a highly endogamous population, “adults with DM [diabetes mellitus] and hypertension associated showed greater hearing impairment” (Bener et al. 2016).

There is an association between chronic alcohol abuse and hearing impairment (Rosenhall et al. 1993), while a protective effect of moderate alcohol consumption has been shown (Fransen et al. 2008).

Hearing impairment is common in idiopathic PD (Vitale et al. 2012), and there are 77% more cases of PD in patients with hearing loss than in those without hearing loss (Lai et al. 2014). An association between incident dementia and hypacusia has been shown (Lin et al. 2011a).

In rats, low doses of a statin (atorvastatin) appear to prevent noise-induced hearing loss (Jahani et al. 2016). In patients with hyperlipidemia, tinnitus may be successfully treated by atorvastatin (Hameed et al. 2014). In mice, another statin (pravastatin) attenuates cochlear injury caused by noise (Park et al. 2012). In a mouse strain with accelerated aging, atorvastatin slows down the deterioration of inner ear function with age and this “suggest[s] that statins could also slow down the age-related deterioration of hearing in man” (Syka et al. 2007). In a rat model for type 2 diabetes, losartan treatment effectively contrasts the hearing dysfunction that is typical in these animals (Meyer zum Gottesberge et al. 2015).

CONCLUSION

The traditional interpretation of aging, based on the tenets of the old paradigm, leads the researchers to justify the many ailments that afflict the elderly as diseases caused by various and different degenerative processes. According to the old paradigm, this implies that the disorders may well have common characteristics when there are identical or similar degenerative factors, but the similarities do not allow at all to consider them as a single disorder with various manifestations. Therefore, aging is explained as the sum and the overlapping of many different diseases and the term “aging” is only a useful term that summarizes them all without indicating a unique and distinct entity. This theoretical conception, among other things, has a practical consequence so that, in the International Classification of Diseases (ICD-10 2016, ICD-9-CM 2016), a code to define aging is nonexistent and so, in the international statistics of the World Health Organization, aging is ignored as a cause of death (World Ranking Total Deaths 2014).

In complete contrast to this classical view, in the interpretation of the new paradigm, the term “aging” indicates a precise and distinct physiological mechanism, genetically determined and

regulated, which manifests itself in all tissues and organs, and in the organism as a whole, as a consequence of a single, specific, and well-defined mechanism. As briefly discussed above, this mechanism originates in the telomere–telomerase–subtelomere system and causes a progressive increase in the fraction of cells in replicative senescence and in various degrees of gradual senescence, with a parallel decline in cell turnover rates and in the functions of tissues and organ, which leads to a condition defined as “atrophic syndrome.”

For all cell types, as well as for the tissues and organs they form and for the functions resulting from them, this decline has two general modes:

- i. Cells subjected to turnover (e.g., nonneuronal cells, gliocytes included, certain types of neuronal cells such as the ORCs) undergo a direct decline
- ii. Cells not subjected to turnover (e.g., most neurons) but dependent on satellite cells that show turnover suffer from a decline in the cells upon which they depend

However, it is useful and necessary to add further considerations that are based on the evidence:

1. Unhealthy lifestyles which cause diabetes, obesity, hypertension, and exposure to toxic substances and other “risk factors” damage cells and accelerate their turnover, causing alterations and anticipation of physiological aging.
2. By avoiding or reducing these “risk factors” and/or by using “protective drugs,” such as ACE inhibitors, sartans, and statins, cellular damage and the associated disorders, caused by slackened or exhausted cell turnover, are avoided or reduced. This occurs both for the decline in cells with turnover (e.g., emphysema caused by alveolocyte turnover failure and arteriosclerosis due to endothelial cell turnover failure) and for the decline in cells without turnover but depending on cells with turnover (e.g., AMD, AD, PD, etc. caused by the decline in their trophic cells).
3. The full avoidance of the risk factors annuls the anticipation or increased probability of the aforementioned diseases but does not cancel the physiological rhythm and characteristics of aging.
4. The alterations of the characteristics of physiological or “normal” aging are definable as diseases if “disease” is conceived as something that causes sufferings but not if “disease” is used in the meaning of alterations shown in a normal condition. Perhaps a more neutral term (e.g., “trouble”) should be used for alterations that are associated with physiological aging.
5. For the troubles of aging, if we disregard the precocious cases due to genetic anomalies, it is difficult to distinguish between the physiological forms (which we must consider as part of physiological aging and are not prevented or modified by a healthy lifestyle and/or protective drugs) and the precocious form, which are due to some risk factor and may be undoubtedly defined as diseases.

These concepts are summarized in Figures 5.1, 5.2, and 5.7 and in Table 5.1.

Now, some important general concepts may be expressed

1. The telomere theory allows a unified and coherent vision of various diseases of the nervous system (e.g., AD, PD, AMD, presbycusis, and age-related hyposmia), which are apparently quite distinct and without a common root.
2. The telomere theory allows a unified and consistent view of these diseases in the framework of a wide range of diseases that are not pertaining to the nervous system. Through this unitary conception, it is possible to have a rational explanation of the noteworthy commonality of factors that increase the risks (risk factors) or reduce them (protective factors) for all the aforementioned diseases.

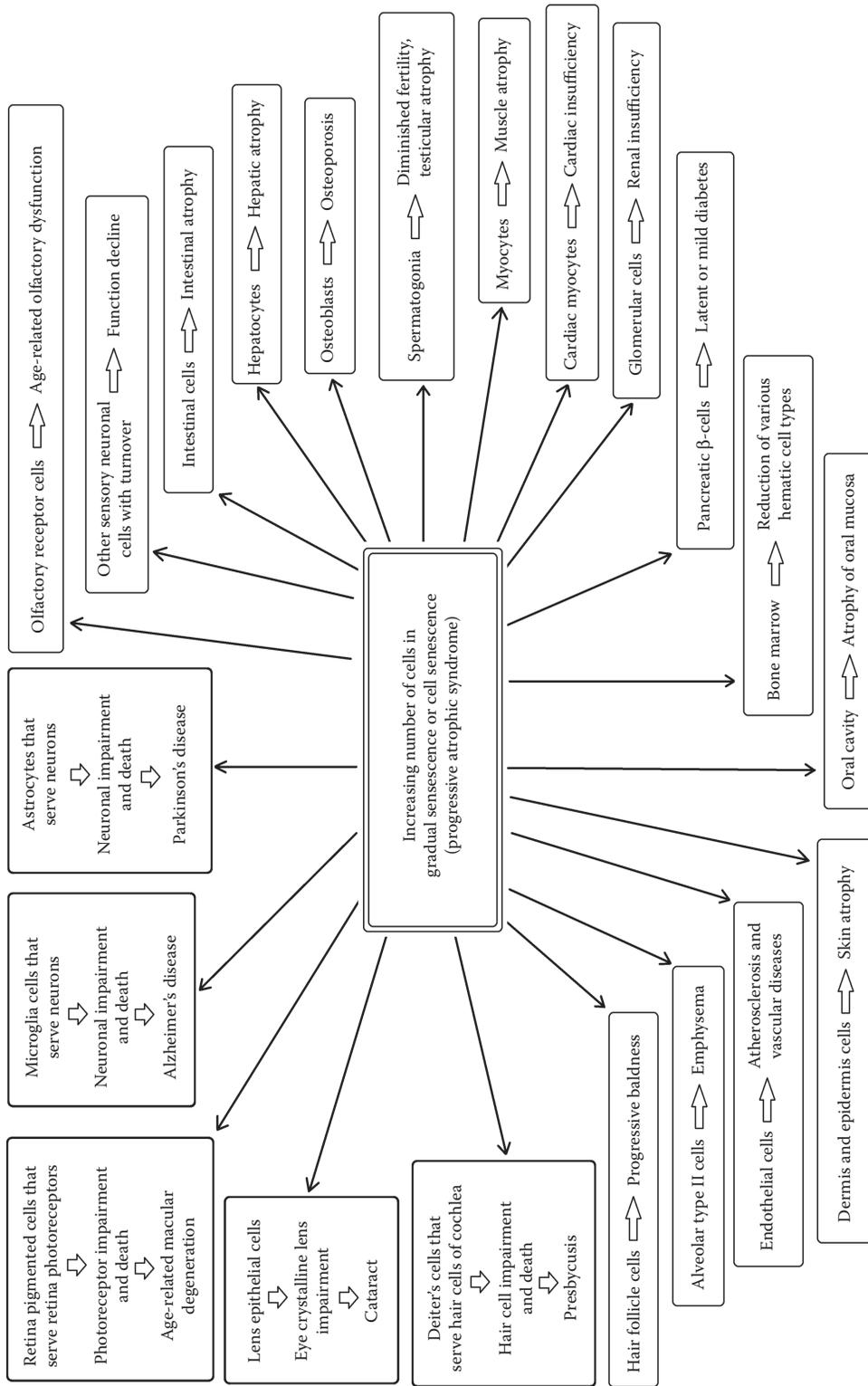


FIGURE 5.7 A scheme of the aging process. Most cell types, including some types of neurons, are subject to turnover. Cell turnover decline causes the progressive impairment of the functions depending on these cells. Perennial neurons are compromised by turnover decline and gradual senescence of essential satellite gliocytes.

TABLE 5.1
Relations between Some Troubles and Some “Risk Factors” or “Protective Drugs”

| Troubles | Cell Turnover | Risk increased (+) or Perhaps Increased (+?) or Lowered (−) or Unaltered (∅) by | | | | | | | | | | Protective Effect by | |
|-------------------------|---------------|---|----------|--------------------------|--------------|-------|--------------|---------------|---------------|---------|-------------------|----------------------|--|
| | | Age | Diabetes | Obesity/ Dyslipidemia | Hypertension | Smoke | Moderate Use | Alcohol Abuse | Alcohol Abuse | Statins | ACE-i, Sartans | | |
| Endothelial dysfunction | Yes | +1 | +2 | +3 | +4 | +5 | −6 | +7 | +8 | +9 | | | |
| Olfactory dysfunction | Yes | +10 | +11 | +12 | +13 | +14 | 15 | +16 | +17 | 18 | | | |
| AMD | No | +19 | +20 | +21 | +22 | +23 | 24 | 25 | +26 | 27 | | | |
| Ad | No | +28 | +29 | +30 | +31 | +32 | −33 | +34 | +35 | +36 | | | |
| PD | No | +37 | +38 | +39 | +40 | −41 | −42 | +43 | +44 | +45 | | | |
| Hearing impairment | No | +46 | +47 | +48 | +49 | +50 | −51 | +52 | +53 | +54 | | | |

Notes: (1–5) Wilson et al. (1987), Hill et al. (2003); (6) Roerecke and Rehm (2014), Gardner and Mouton (2015), de Gaetano et al. (2016), (7) Gardner and Mouton (2015), de Gaetano et al. (2016), (8) Walter et al. (2002), Su (2015), (9) Su (2015), (10) Schubert et al. (2012), Doty and Kamath (2014), Gouveri et al. (2014), (11) Gouveri et al. (2014), Mehdizadeh et al. (2015), (12) Richardson et al. (2004), Patel et al. (2015), (13) Gouveri et al. (2014), (14) Vent et al. (2003), (15) No specific study; (16) Rupp et al. (2004), (17) Kim et al. (2012), (18) No specific study; (19) Rudnicka et al. (2012), (20–22) Klein et al. (2007), Mares et al. (2011), (23) Klein et al. (2007), Armstrong and Mousavi (2015), (24) Armstrong and Mousavi (2015), (25) Klein et al. (2010), (26) Gehlbach et al. (2015), (27) No specific study; (28) Gorelick (2004), (29) Rosendorff et al. (2007), Baglietto-Vargas et al. (2016), Rani et al. (2016), Vicente Miranda et al. (2016), (30) Rosendorff et al. (2007), Wanamaker et al. (2015), (31) Rosendorff et al. (2007), Qiu et al. (2005), Michel (2016), (32) Rosendorff et al. (2007), Durazzo et al. (2014), (33) Campdelacreu (2014), Ilomaki et al. (2015), (34) Rosendorff et al. (2007), Campdelacreu (2014), (35) Vogel et al. (2006), Ellul et al. (2007), Wanamaker et al. (2015), (36) Vogel et al. (2006), Ellul et al. (2016), (37) De Lau and Breteler (2006), Pringsheim et al. (2014), (38) Hu et al. (2007), Tomlinson and Gardiner (2008), Zhang and Tian (2014), Vicente Miranda et al. (2016), (39) Abbott et al. (2002), Hu et al. (2006), Zhang and Tian (2014), (40) Zhang and Tian (2014), (41) Li et al. (2015), (42) Ishihara and Brayne (2005), (43) Eriksson et al. (2013), (44) Gao et al. (2012), Friedman et al. (2013), Undela et al. (2013), Sheng et al. (2016), (45) Lopez-Real et al. (2005), Sonsalla et al. (2013), (46) Zhan et al. (2010), Lin et al. (2011b), (47) Akinpelu et al. (2014), Oron et al. (2014), Calvin and Watley (2015), Helzner and Contrera (2016), Bener et al. (2016), (48) Franssen et al. (2008), Oron et al. (2014), (49) Oron et al. (2014), Przewozny et al. (2015), Bener et al. (2016), (50) Cruickshanks et al. (1998), Franssen et al. (2008), Oron et al. (2014), Chang et al. (2016), (51) Franssen et al. (2008), (52) Rosenthal et al. (1993), (53) Syka et al. (2007), Park et al. (2012), Hameed et al. (2014), Jahani et al. (2016), (54) Meyer zum Gottesberge et al. (2015).

3. The possible criticism against the telomere theory, and consequently against the programmed aging paradigm, caused by the evidence of tissue and organs largely composed of cells without turnover and that age, is overcome by the evidence previously expounded. Conversely, the telomere theory and the programmed aging paradigm emerge strengthened from the overcoming of such criticism.
4. If aging is a physiological phenomenon, genetically determined and regulated, in principle it could be regulated, slackened, or even cancelled. This statement, which might seem unrealistic and, for the supporters of the non-programmed aging paradigm, the declaration of something clearly utopian, that is, impossible, on the contrary, is something that has been proved: (i) since 1998, it is known that in cultivated normal cells, telomerase activation leads to longer telomeres and cancels all the manifestations of cell senescence, both the biochemical alterations and the incapacity to duplicate (Bodnar et al. 1998; Counter et al. 1998; Vaziri 1998; Vaziri and Benchimol 1998); (ii) telomerase reactivation in aged mice with blocked telomerase determined the clear reversal of all the manifestations of aging, those of the nervous system included (Jaskeliouff et al. 2011); (iii) in one- and two-year-old normal mice, telomerase reactivation delayed the aging manifestations and increased the life span (Bernardes de Jesus et al. 2012); (iv) human skin obtained from aged fibroblasts with reactivated telomerase was not distinguishable from skin obtained from young fibroblasts (Funk et al. 2000).
5. In the search for a treatment to slacken or reverse aging, attention should be focused on the telomere–telomerase–subtelomere system. Telomerase reactivation has been proposed as treatment for AD (Fossel 1996, 2004) and for AMD (Libertini 2009b). As an intermediate step for the goal of a complete control of aging, the effective treatment of diseases that are strongly invalidating and expensive, such as AD, PD, and AMD, by actions on the telomere–telomerase–subtelomere system has been proposed (Libertini and Ferrara 2016a).

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