TEXTBOOK OF GERIATRIC DENTISTRY

THIRD EDITION

Edited by
Poul Holm-Pedersen
Angus Walls
Jonathan Ship

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Textbook of geriatric dentistry

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Preface

Third edition, 2015

When the first edition of *Textbook of Geriatric Dentistry* was published almost 30 years ago, it was one of the first books ever on this topic; maybe it really was the very first international book addressing the topic in a broader perspective, not just "dentures for old people". The prefaces of the first and second editions of the book tell some of the history of geriatric dentistry and its development over three decades. The topics extend from basic biological, cellular, physiological, psychological and social aspects of aging, with special attention to the clinical problems of oral health care for older adults. This new edition also addresses comprehensive aspects of medical and psychosocial conditions, as well as aging in a life-course perspective, all of which have an impact on oral health care and well-being in old age. In addition, this volume includes chapters on palliative care at the end of life, pain management and long-term care.

In preparing the book it has been a privilege to work with some of the world's most distinguished scientists and clinicians. Sadly, four of our authors have passed away much too early during the production of this book: Kirsten Avlund, Jane Chalmers, Asuman Kiyak and Jonathan Ship, the latter also co-editor of this new edition. They will never see their chapters published. This book is dedicated to the memory of these authors. Their death is a great loss for their families and close friends, and for the entire community of gerontology scholars. We also want to pay a special tribute the co-editor of the two first editions of the book, Harald Löe, former Director, National Institute of Dental and Craniofacial Research (NIDCR), Bethesda, who died in 2008.

Poul Holm-Pedersen and Angus W. G. Walls
April 2015

Preface

Second edition, 1996

The first edition of *Geriatric Dentistry — A Textbook of Oral Gerontology* appeared in 1986. During the 10 years past, the demographic trends have continued to bring attention to the greying of the populations in industrialized countries. Also, in the course of the last decade, much of the scientific research – and especially that dealing with molecular biology – has provided new information on genetic governance and environmental mechanisms inherent to the life and death of the cells.

A vast number of scientific articles on the psychosocial and somatic needs of the aging macroorganism, and their clinical implications, has been published in more and more journals.

It is now time for summation and interpretation.

Thus, important objectives of this edition are to provide to the reader a comprehensive and convenient account of the complex issues of aging, to produce an assembly of the current concepts of systemic and oral disorders in the aging patient, and present the means to their solution or amelioration, with the full realization that these challenges can only be met by basic knowledge and clinical competence.

It has been said that the evolution of a profession is evidenced by the scope and quality of its literature. It is our hope that this text might be a small contribution to this principle. However, the merit of this edition, we feel, lies in the wide expanse and penetrating depth with which each of the authors approached the topics.

Poul Holm-Pedersen and Harald Löe
January 1996

Preface

First edition, 1986

Some of the world's great artists have depicted the face of old age. *Leonardo's* sketchbooks illustrate the gnarled features, the wrinkles, the compressed lips, and the sunken jaws of the elderly. Rembrandt's self-portraits similarly record in meticulous detail the lines, the changes in pigmentation, and the moles that mark the aging skin. Today we seek the cellular and molecular changes in the oral tissues that underlie these signs of age.

This search is given extra emphasis by the dramatic increase in the proportions of older people in the populations of all industrialized countries. This trend is expected to continue, with the result that the elderly as a segment of society with special abilities as well as special needs, will become increasingly prominent.

In the industrialized world the new generations of elderly will be better educated and more demanding of social and health services than past generations. Many will retain their natural teeth; only a minority will wear complete dentures. These changes in health status, in attitude and behavior, will have a significant impact on oral health needs, creating new challenges for the dental profession.

The prevention and treatment of oral and dental diseases require a thorough knowledge of the biological variables influencing disease patterns in the aging patient. The relationship between oral and general health and the effects of chronic ailments and diseases on the ability of the older patient to accept treatment must be understood if dental health care is to have a reasonable chance of success. Dentists of tomorrow will need a broader range of knowledge, clinical skills, and human understanding to recognize and treat the oral health problems of their older patients. Cognizant of these needs, special courses and programs in dentistry for the elderly are being included in many undergraduate and graduate dental school curricula.

The objective of this book is to provide a comprehensive review of the processes of aging and their relevance to the delivery of dental health care. Its target audiences are undergraduate and postgraduate students as well as practicing clinicians. The chapters cover the biological, psychological, social and medical aspects of aging, with particular attention to the clinical problems of dental care of the aging patient. The title, *Geriatric Dentistry — A Textbook of Oral Gerontology,* was chosen because the term "geriatric dentistry" is an accepted name for the discipline. However, the book is not restricted to the "geriatric patient", but addresses virtually every aspect of oral health of the elderly, including normal and pathological changes associated with aging. Therefore, the term "oral gerontology" has been adopted to reflect the interdisciplinary character of this subject and to emphasize clinical management in a broader sense. It is our hope that it will contribute to a better understanding of the many facets of dental care for the aged and that it may prove useful to clinicians, health professionals, and researchers within geriatric dentistry and related disciplines.

Pout Holm-Pedersen and Harald Löe
1986

CHAPTER 1

Demography – impact of an expanding elderly population

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Introduction

Scientists who study the demography of aging investigate trends in, and characteristics of, fertility, mortality and migration and how these components of population change influence, and are influenced by, the environments in which people live. This is a new area of scientific inquiry because aging, as a uniquely demographic phenomenon of populations, has been experienced on a large scale by only one species – humans – and even then only for the last century. Among the many social and economic changes that population aging has brought forth, one of the most important has been dramatic increases in the absolute number of people who live into older regions of the lifespan – a phenomenon that will accelerate in the coming decades.

It is important to understand the difference between population aging and individual aging. Individual aging refers to the biological changes that occur in our cells, tissues and organs with the passage of time, and it is measured demographically at the level of the individual by the duration of our lives. By contrast, population aging is characterized by shifts in the age structure of groups of people such that the relative proportion of older persons (often defined by those aged 65 and older) increases in relation to the number of people under the age of 65. The most common measures that are used to track changes in population aging across time or between population subgroups include the median age, expected remaining years of life (i.e. life expectancy) at middle and older ages and the percentage of the total population aged 65 and older.

Causes and consequences of population aging

For most of recorded history there has been a consistent (stable) pattern of fluctuating birth rates and death rates. Until about the middle of the 19th century, death rates had consistently fluctuated between peaks and troughs as a result of communicable diseases that periodically decimated populations, followed by times of relative stasis. Birth rates were extremely high during most of human history. On average, women gave birth to about seven babies during their reproductive years. Many of the children died in their first year of life from communicable diseases, but death rates were also extremely high throughout the age structure. In fact, the risk of death was so high at middle and younger ages that survival into older ages (beyond age 65) was a rare event by comparison to survival patterns observed today. Living into extreme old ages (ages 85 and older) was an extremely rare occurrence. Since birth rates have almost always exceeded death rates by a small margin throughout most of our history, the size of the human population has grown steadily for thousands of years.

If you were to count the number of people alive at all ages in a given year and plot them on a graph, what you would see is a characteristic age distribution that resembles the shape of a pyramid (see Figure 1.1). This is a common age pattern among humans and many other forms of life where there are a large number of young followed by progressively fewer middle aged and older members of the population. In a hypothetically closed population with no migration, the horizontal bars in the age pyramid reflect the number

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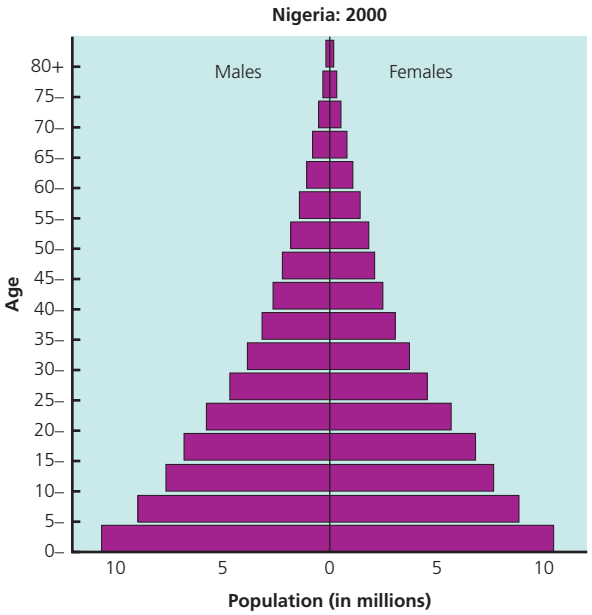

Figure 1.1 Age pyramid for humans in Nigeria in the year 2000. *Source:* United Nations, 2001.

of people surviving to each age range from an original birth cohort based on prevailing death rates. However, in an open population with migration and changing vital rates (which reflect the true nature of living conditions), the age pyramid reflects historical patterns of fertility, mortality and migration. The age pyramid is what characterized the human age distribution throughout most of our history, but this changed rapidly during the 20th century.

During the last 100 years a combination of events led to dramatic changes in the stable patterns of birth rates and death rates that had likely existed for thousands of years. Advances in public health led to the availability of clean water and refrigeration, sewage disposal and improved living and working environments. These developments combined with modern medicine to significantly reduce the transmission of, and death rate from, air- and water-borne infectious diseases. Within a single generation the environmental conditions that permitted the easy transmission of diseases that killed infants and children and women during childbirth were profoundly altered. From a biological perspective, modifications of this magnitude and importance suggest that fundamental changes in the forces of natural selection operating on the human species had occurred.

As the risk of death at younger ages declined rapidly, the high birth rates that were needed to replace the children who died from infectious diseases began to subside. Since the decline in birth rates lagged behind the decline in death rates, the result was rapid population growth during the 20th century – from one billion in 1900 to more than 6.5 billion by the turn of the 21st century. The eventual transformation of birth rates and death rates to the lower levels now observed in most developed nations is what set the stage for the demographic phenomenon of population aging.

When death rates declined at younger ages, the base of the age pyramid expanded and its apex became smaller by comparison. When the apex of an age pyramid decreases relative to its base, it may be said that a population is becoming younger. Thus, the first demographic consequence of declining early-age mortality was a younger population. However, within a single generation those saved from dying at younger ages began to reach middle and older ages, thereby altering the population's age composition by increasing the size of the middle and apex of the age pyramid relative to its base (see Figure 1.2). When death rates at younger ages stabilize at extremely low levels, as they have in all countries with high life expectancies, the base of the age pyramid then becomes sensitive only to changes in birth rates. With a stable base and a growing middle and apex, a permanent shift in the age structure occurrs from its historical pyramid shape to that of a square-like or rectilinear form. Although temporary increases in birth rates (like those observed in the post-World War II era) can slow population aging and even temporarily reverse it, the new rectilinear age structure will eventually reassert itself as the children from the larger birth cohorts survive to older ages. The transformation from stable high birth and death rates to stable low birth and death rates has led to permanent changes in the age structure of the human species.

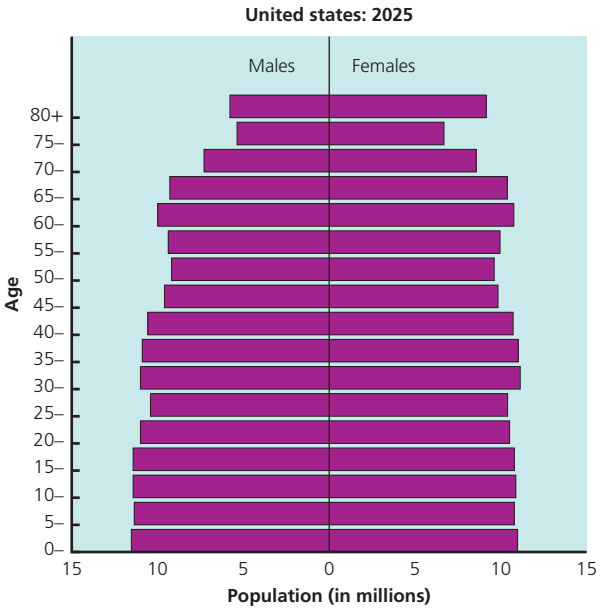

Figure 1.2 Age pyramid of the future with a shift in the historical pyramidal shape to that of a square-like or rectilinear form. *Source:* United Nations, 2001.

The social, economic and health implications associated with population aging are profound. Consider an ongoing debate in the health and demographic sciences known as the compression versus expansion of morbidity hypotheses. When death rates decline at younger ages the proportion of each birth cohort surviving past ages 65 and 85 increases rapidly. By way of example, in France the proportion of the female birth cohort of 1900 that was expected to survive to ages 65 and 85 based on death rates in that year was 39% and 3.5%, respectively. By comparison, the female birth cohort of 2000 is expected to have 90% and 50% survive past ages 65 and 85, respectively. These unprecedented patterns of survival into older ages are now common throughout the nations of the developed world, and they have led scientists to track the health of these aging pioneers and how prospective changes in death rates at older ages might influence the future health of the older population.

One school of thought argues for what has come to be known as the compression of morbidity hypothesis. With this hypothesis it is suggested that lifestyle changes and advances in medicine will continue to reduce the risk of death from fatal diseases and simultaneously lead to a postponement in the onset and age progression of the nonfatal disabling diseases. The premise of this theory is that there is a fixed biological limit to life towards which populations are headed, and as improved lifestyles successfully postpone the onset and expression of fatal diseases and nonfatal but highly disabling diseases and disorders, more people will be pushed towards their biological 'limit' to life, and morbidity and disability will be compressed into a shorter duration of time before death.

A second school of thought proposes what has come to be known as the expansion of morbidity hypothesis. The proponents of this hypothesis maintain that the forces influencing the onset and age progression of nonfatal diseases associated with senescence are mostly independent of the forces influencing the risk of death from fatal diseases. If death rates from fatal diseases continue to decline, it is hypothesized that the saved population will be exposed to a longer duration of time during which the nonfatal but highly disabling diseases and disorders of senescence have the opportunity to be expressed. In other words, the extension of life resulting from continued progress made against fatal diseases is hypothesized to eventually prolong the period of disability in old age among future cohorts of older persons.

A debate has taken place in the scientific literature regarding these two important hypotheses. Although the evidence suggests that in the 1980s several countries were experiencing an expansion of morbidity, since then there is evidence to suggest that some compression has been occurring. However, research in this area should be interpreted with caution because empirical studies addressed to this debate have focused on health transitions observed only during the recent past (since 1980). It is distinctly possible that future cohorts of older persons will be notably different in many ways from current older generations because of the high degree of selection that occurred among people living to older ages in today's world. Furthermore, it is not possible to know with any degree of certainty whether the health status of future cohorts of older persons will be better or worse than previous cohorts passing through the same ages.

Relationship between individual aging and population aging

The transformation of birth rates and death rates to currently stable low levels was caused, in part, by the same forces of declining mortality that contributed to unprecedented increases in life expectancy. During the Roman Empire life expectancy at birth was estimated to be about 28 years. By 1900 life expectancy for men and women combined had increased to 45 years in the nations with the lowest death rates at that time, but by the 21st century life expectancy at birth has risen to between 75 and 80 years. Most of the gains in life expectancy during the mortality revolution of the last century are a product of declining early age mortality, but notable reductions in middle and old age mortality have been observed in recent decades. In today's high life expectancy populations of North America, Western Europe, Scandinavia and Japan, death rates at younger ages have declined to such low levels that 98 out of every 100 babies born will live past the age of thirty.

As life expectancy continues to rise due to further expected reductions in middle and old-age mortality, survival into increasingly older regions of the lifespan by larger segments of the population is inevitable. Thus, life-extending technologies and lifestyle modification that bring forth declining death rates contribute to population aging by further expanding the apex of the age pyramid relative to its base. How much higher life expectancy can rise is a question of great interest and debate among scientists today, but one thing most can agree on for now is that population aging is an inevitable demographic phenomenon that will be accelerated by anticipated reductions in the risk of death.

Population aging and geriatric dentistry

In the last century the unprecedented aging of humanity has enabled modern populations to witness something that was rarely observed in the history of our species – old age and

the diseases and disorders that accompany it, as well as the wisdom and benefits that accompany healthy survival into regions of the lifespan rarely experienced by our ancestors. At one level we have taxed our bodies to their limits, exposing our joints, muscles, bones, teeth and brains to decades more use than any previous human population. We have come to better understand the limitations of our bodies and how some components, such as neurons, muscle fibers and tooth enamel, do not replicate during the course of life. In a very important way, some components of our bodies that are critical to survival, such as muscles and neurons, represent limiting factors that will preclude a further dramatic extension of life unless it becomes possible to alter their rates of decline with age. However, we have also come to learn that there is no aging or death program for humans, which means that in many important ways it is possible to influence the way in which we age as individuals, and thus the degree to which individual aging influences population aging.

Dentistry will influence, and will be affected by, the demographic phenomenon of population aging and its antecedent causes in several ways. Population aging is defined, in part, by the extension of the lives of millions of people into their 8th, 9th and 10th decades of life who would ordinarily have never lived that long had they not been born in the modern era. As the extremely large baby boom cohorts of the post-World War II era move through the age structure and reach retirement ages, the unique health care needs of this population are going to challenge health care systems across the globe. The demand for geriatric dentistry will parallel the rising demand for all of the health care fields. It is also worth noting that younger generations might need less geriatric dentistry as they grow old since these birth cohorts were exposed to fluoridated water.

At one level, dentistry is unique in public health because it is known that, with sufficient preventive maintenance, it is possible to retain our teeth at a high level of functional performance for most of our lives. In other words, it may very well be possible that among most people, when properly maintained, teeth can outlast most other components of the human body. The same cannot be said for muscle mass and neurons, both of which are known to respond well to use, but which still experience significant functional declines no matter how hard we try to maintain them at younger ages. Furthermore, even with the loss of our natural teeth, it is possible to indefinitely maintain functionality with prosthetics. The same cannot be said for most other parts of the body.

Dentistry is also unique in its effect on population aging because primary prevention practiced in our early and middle ages can not only help to maintain oral health, such practices may also reduce the risk of a number of chronic fatal diseases throughout life – the most important among them is heart disease. Thus, the field of dentistry has the potential to reduce the risk of death at older ages, extend the duration of life, and thereby further accelerate the demographic phenomenon of population aging. However, geriatric dentistry in the 21st century will not be without its challenges. With many more people living into extreme old ages (e.g. beyond age 100) where only a small segment of the population used to survive, geriatric dentistry will face health issues associated with the systemic aging of other components of the body – most notable among them are bone density and immune surveillance.

Like many other public health fields, dentistry will be profoundly influenced by the demographic changes in the population that have already taken place and those that are forthcoming. It may very well be true that the health and aging of the entire body is visible through the lens of the mouth, so dentists have the ability to monitor the health status of their patients at a higher level of frequency than primary care physicians. Dentistry in the 21st century will maintain its position as a central component to public health and will no doubt further contribute to the extension of life and an anticipated acceleration in population aging.

Further reading

Dublin, L.I., Lotka A.J. & Spiegelman M. (1949) *Length of life: study of the life table*. Ronald Press, New York.

Finch, C.E. & Crimmins, E.M. (2004) Inflammatory Exposure and Historical Changes in Human Life-Spans, *Science*, **305**, 1736–1739.

Fries, J.F. (1989) The compression of morbidity: near or far? *The Milbank Quarterly*, **67**, 208–323.

Hayflick, L. (2000) The future of ageing. *Nature*, **408**, 267–269.

Himes, C. (2005) *Elderly Americans. Population Bulletin*. Population Reference Bureau, Washington, DC.

Kinsella, K. & Velkoff, V.A. (2001) *An Aging World: 2001*. US Census Bureau, Series P95/01-1, US Government Printing Office, Washington, DC.

Kirkwood, T.B.L. (1992) Comparative life-spans of species: Why do species have the life spans they do? *American Journal of Clinical Nutrition*, **55**, 1191S–1195S.

Kirkwood, T. & Finch, C. (2000) *Chance, Development and Ageing*. Oxford University Press, New York, NY.

Macdonell, W.R. (1913) On the expectation of life in ancient Rome, and in the provinces of Hispania and Lusitania, and Africa. *Biometrika*, **9**, 366–380.

Martin L.A. & Preston S.H. (eds) (1994) *Demography of Aging*. National Research Council, National Academy Press, Washington, DC.

McNeill, W.H. (1976) *Plagues and Peoples*. Anchor, Garden City.

Olshansky, S.J. & Ault, B. (1986) The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *The Milbank Quarterly*, **64**, 355–391.

Olshansky, S.J., Carnes B. & Cassel C. (1993) The aging of the human species. *Scientific American*, **268**(4), 46–52.

Olshansky, S.J., Carnes, B.A. &, Butler, R. (2001) If Humans Were Built to Last. *Scientific American*, **284**(3), 50–55.

Omran, A. (1971) The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. *Milbank Memorial Fund Quarterly*, **49**, 509–538.

Perls, T., Silver, M.H. & Lauerman, J.F. (2000) *Living to 100: Lessons in living to your maximum potential at any age*. Basic Books, New York, NY.

Rowe, J.W. & Kahn, R.L. (1987) Human aging: usual and successful. *Science*, **237**(4811), 143–149.

United Nations. (2001) *World population prospects: the 2000 revision*. United Nations, New York, NY.

Williams, G.C. (1957) Pleiotropy, natural selection and the evolution of senescence. *Evolution*, **11**, 398–411.

CHAPTER 2

Biological and physiological aspects of aging

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We are currently experiencing an unprecedented change in the age structure of our societies, as average life expectancy continues to increase at a staggering rate of 2 years every 10 years, which means 5 hours every day. In the developed world the fastest growing population group is the people over 80 years old. The world's population over 65 years old is currently growing at a rate of 2.4 per cent per year, which is actually faster than the global total population.

The increases in life expectancy, which began in the mid-1800s, can be explained by dramatic changes in the familial, social, economic and political organization of societies but more importantly by improvements in medicine and sanitation. These demographic changes represent a major challenge for both clinicians and scientists alike, since it becomes imperative to understand the nature of the aging process and how to deal with the medical problems of the increasing elderly population. Currently, we are beginning to understand why aging occurs and what molecular mechanisms are involved in the aging process.

The primary objective of this chapter is to elucidate the molecular mechanisms involved in the aging process and how these impact on organ physiology, in particular the oral environment.

What is aging and why does it occur?

Aging is a progressive generalized impairment of function resulting in a loss of adaptive response to stress and in a growing risk of age-associated disease. The overall sum of the changes occurring with aging increases the probability of dying within the population.

It was first noted by Gompertz (1825) that, in humans, cohort mortalities show an exponential rise with increasing chronological age [1].

Regardless of the specific mechanisms behind aging, there are three different views of its origins. One view is that aging simply occurs, and that natural selection has played no important part in its genesis. It is suggested that, like any man-made machine which inevitably decays and becomes dysfunctional with time, living organisms suffer age-dependent **wear and tear**.

Two other views propose that natural selection played a crucial role in the process. One comprises the so-called **adaptive theories** of aging, which state that aging has some sort of direct competitive advantage and that it is programmed in a similar way to development. There are several lines of evidence which show that these theories do not make sense from an evolutionary point of view. One of the main objections is that there is little evidence from natural populations that aging is a significant contributor to mortality in the wild. Data available from populations in the wild show that mortality in the early and middle periods of life is usually quite high, preventing many individuals from surviving long enough to experience aging. There are of course exceptions to the general rule, particularly in larger mammals, but it is well established that even in these cases the number of individuals reaching old age is very small. So, the argument that aging could have evolved to prevent old individuals from competing for resources with younger individuals does not stand on firm ground, as Figure 2.1 illustrates.

One of the other arguments that has been presented in support of programmed aging is that there is a clear heritable

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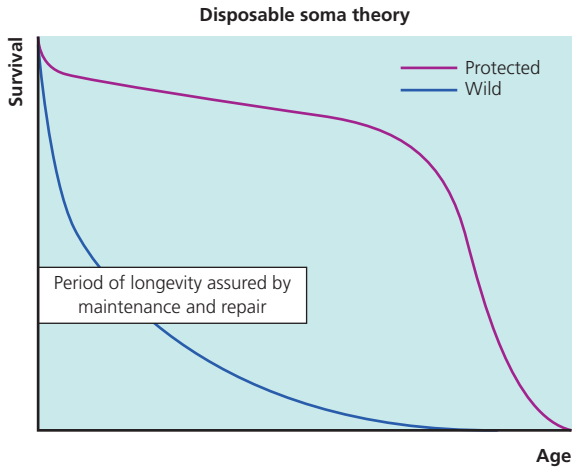

Figure 2.1 Evidence supporting the disposable soma theory of aging: the survival curve of a wild population tends to show little sign of age-associated mortality, which only becomes apparent when the population is in a protected environment.

component to human aging and also that in recent years large numbers of genes affecting longevity have been identified. For instance, in the nematode *Caenorhabditis elegans* several mutations have been identified that lead to substantial extension of the organism's lifespan [2]. However, it has also been argued that many of these genes are involved in pathways involved in resistance to stress and maintenance of these organisms. Moreover, even when the environment and genes are the same, individual nematodes show remarkable variation in terms of aging phenotypes and lifespan [3].

Another contrasting view suggests that aging is not adaptive and has evolved as an indirect consequence of natural selection. One widely accepted version of this view is the '**disposable soma theory**', which suggests that aging is a consequence of natural selection maximizing resources in maintenance of germ cells to the detriment of somatic cells, thereby allowing age-dependent damage of the latter. This view supports the idea that wear and tear does occur as we age, but that this is more a consequence of resource allocation rather than simple inevitable time-dependent decay. There is growing evidence that maintenance mechanisms fail with aging, as we shall discuss in the next section.

Aging of cells: molecular mechanisms of aging

We are now starting to understand why the decline in function associated with aging occurs. However, what the mechanisms involved are is not yet clear. Currently, several components within the cells have been identified which are particularly susceptible to 'wear and tear' and to the apparent failure of maintenance mechanisms within cells which occurs as we age.

We will now examine the various proposed molecular mechanisms which impact on the aging process.

Somatic mutation and DNA damage theories

The idea of aging being caused by a loss of ability to repair cellular components has been the basis of the concept that chromosomal abnormalities might underlie the aging process. This idea can be dated back to 1959, when Szilard postulated that lifespan might be determined by the rates of random chromosomal 'hits' which render 'all genes carried by that chromosome inactive'. He assumed that the rate of 'hits' would be constant throughout life and would lead to an age-dependent decrease in the number of functional cells. Although Szilard's notion of major chromosomal hits has not withstood detailed examination, it is reasonable to assume that processes that interfere with the integrity of somatic cell DNA will lead to a loss of function of cells.

The modifications to which DNA may be subjected can be of two types: mutations and damage. Mutations are any changes in the sequence of genomic DNA and can be of three sorts: **point mutations**, which occur when only a single DNA base pair is changed; **deletions**, which occur when DNA base pairs are deleted from the genome and **insertions**, which occur when sequences of DNA (often so-called 'transposable elements') move from one region of the genome into another. DNA damage, on the other hand, refers to any chemical alterations occurring in DNA which do not affect the polynucleotide sequence. These include pyrimidine dimers, single and double strand breaks, covalent cross-linking of DNA strands, oxidative modifications of certain nucleotides, and so on.

DNA damage is a common occurrence in mammalian cells. Measurements by various groups have indicated that in humans more than 10 000 oxidative modifications of DNA occur per cell per day [4]. If such damage remained unrepaired, one would expect that the cells would become non-functional in a very short period of time. Luckily for us, for each specific type of damage that can occur in DNA there is also an enzyme which is able to repair it. The repair ability of DNA differs between species and cell types. For instance, it has been shown that embryonic stem cells, which are undifferentiated cells able to divide without apparent limit, have better DNA repair capability than their differentiated daughters [5]. These differentiated daughter cells lose their capacity to regenerate indefinitely, mostly due to loss of telomerase activity, an enzyme able to elongate telomeres (see below).

Moreover, a correlation between lifespan of different species and the ability to repair DNA has been observed in various independent studies. In the first study made,

Hart and Setlow (1974) established primary fibroblast cultures from seven mammalian species and then irradiated them with ultraviolet light in order to generate DNA damage. Then, they measured the extent of DNA synthesis outside the S phase from the cell-cycle (unscheduled DNA synthesis), which depended on the incorporation of 3H-thymidine into DNA [6]. The results clearly showed a relationship between longevity and the extent of DNA repair. Other groups have subsequently confirmed an association between DNA repair capacity and longevity, although it must also be noted that differences in body size contribute part of this association.

Also striking, was the finding by Ames in 1994 that the extent of DNA damage products present in the urine of different species was directly proportional to the animals' oxygen consumption [7]. From these results it was concluded that oxidative damage could be a major cause of DNA damage. These results linked DNA damage to oxidative stress which we will discuss in the next section.

The oxidative stress theory of aging

With the exception of a few organisms which are adapted to live under anaerobic conditions, the majority of animals and plants require molecular oxygen in order to produce energy. Oxygen is, therefore, essential in the energy producing reactions which enable the subsistence of life as we know it. However, it is also known that exposure to higher concentrations of oxygen than the ones present in air, is toxic to animals and plants.

Different animal species consume oxygen differently and have different **respiratory quotients (RQ)**, which can be calculated as a ratio of CO_2 produced versus O_2 consumed. This quotient measures the inherent composition and utilization of carbohydrates, lipids and proteins as they are converted to energy and can be used as an indication of the metabolic rate.

In 1928 Raymond Pearl proposed that lifespan varies inversely with **basal metabolic rate** (the 'rate of living hypothesis') [8]. This was supported by the observation that animals appear to have a fixed quota of heartbeats. If the heart rate of a mouse was multiplied by its lifespan, a number would be obtained that is similar to most other mammals. This *metabolic* theory, together with others in the beginning of the 20th century, was based on the finding that an inverse relationship existed between lifespan and metabolic rate. However, no mechanistic interpretation was presented until almost 20 years later, to explain why this relation occurred.

Denham Harman was the first to associate **free radicals** with aging [9]. Free radicals are very reactive chemical species mostly derived from molecular oxygen, which have an impaired electron on the outer orbital. Previous work had shown that ionizing radiation could produce free radicals and that exposure to radiation limited lifespan. Harman established a connection between data showing that irradiation of living systems induces mutation, cancer and aging through production of free radicals and indirect data that free radicals are produced normally in living tissues.

Harman also reasoned that the most likely source of free radicals would be respiratory enzymes that utilize molecular oxygen (particularly those containing iron), the action of catalase on hydrogen peroxide and the splitting of water. However, no direct evidence at that time supported the existence of free radicals in living cells. Only 13 years later, with the discovery of a highly specialized enzyme able to convert superoxide anion in water and hydrogen peroxide (superoxide dismutase), was the importance of endogenous free radicals firmly established [10] and a role in the aging process reconsidered.

Have we acquired enough evidence to support Harman's idea? Are free radicals responsible for aging? Oxygen metabolism does lead to production of reactive oxygen species, but cells possess antioxidant defences able to eliminate them. So perhaps aging could be caused by a progressive failure in the defence system and not by pro-oxidant generation. Actually, two schools of thought exist, one that favours the rate of aging being dependent on the level of antioxidant defences and the other on the level of reactive oxygen species produced. Orr and Sohal (1994) reported the first direct evidence that increased levels of antioxidant enzymes, particularly cytosolic CuZn-superoxide dismutase (CuZn-SOD) and catalase, could together extend medium and maximum lifespan, confer greater resistance to ionizing radiation and oxidation of proteins and DNA in the fruitfly *Drosophila melanogaster*. An earlier study had already shown that *Drosophila* lacking cytosolic CuZn-SOD suffered a significant reduction of lifespan [11], supporting the importance of antioxidant defences in the aging process. There are many conflicting data concerning the way antioxidants affect lifespan. Several studies overexpressed CuZn-SOD and found no significant increase in lifespan in *Drosophila* [12, 13], while others showed lifespan extensions of 33 to 40% [14, 15]. However, recently, these latter experiments have been questioned, due to the fact that an insufficient number of control strains were used, and that controls had artificially short lifespans [16, 17]. More recently, a study was conducted where various combinations of antioxidant genes were overexpressed simultaneously in relatively long-lived *Drosophila* strains, a greater number of control strains was used, but no extension of lifespan was observed in any case [18]. This result can be seen as evidence against antioxidant defences being a limiting factor in aging, at least in lower organisms.

Studies in mice have also proved inconclusive. For instance, mice carrying a heterozygous deletion of the mitochondrial superoxide dismutase, an enzyme able to convert superoxide

anion in water and hydrogen peroxide, showed indications of increased oxidative stress and high cancer incidence but not accelerated aging [19]. However, a recent study showed that targeting catalase (an antioxidant enzyme able to convert hydrogen peroxide into water) to mitochondria increased the lifespan of transgenic mice [20].

The role of mitochondria in aging

Mitochondria are the 'power houses' of aerobic eukaryotic cells and have also been implicated as having a role in the aging process. Mitochondria have two membranes: one which surrounds the entire organelle (the outer membrane) and an inner membrane possessing infoldings called cristae. Embedded in the inner membrane, mitochondria possess enzymes that together catalyse the oxidation of organic components by molecular oxygen (O_2). These oxidations are used to generate ATP, which is the major energy-carrying molecule in cells. Mitochondria produce more than 90% of the ATP that cells require for survival.

However, there is a price to pay for the utilization of oxygen and its reduction into water by electrons carried through the respiratory chain. Incomplete reduction of molecular oxygen can generate univalently reduced oxygen $O_2^{\cdot}$ or superoxide radicals, which can in turn be converted into other reactive oxygen species which damage the major cellular macromolecules such as proteins, lipids and carbohydrates.

In addition to energy production, mitochondria perform multiple functions which are essential for a cell, such as the maintenance of intracellular homeostasis of calcium ions (they act as calcium buffers). They also have a role in triggering programmed cell death (apoptosis).

Mitochondria possess their own DNA, and each mitochondrion contains several copies of this mtDNA, which is maternally inherited. MtDNA is a circular loop 16 569 base pairs long and encoding 13 proteins (which are subunits of the electron transport chain), 22 transfer RNAs and 2 ribosomal RNAs (which are necessary for protein synthesis within the mitochondria). Mutations have been shown to occur in mtDNA leading to several pathologies. Since there are several copies of mtDNA in each mitochondrion, a 'heteroplasmic' condition can exist when both mutant and wild-type mtDNA coexist in the same cell. However, a 'homoplasmic' condition exists when only wild-type or only mutant mtDNA exist in a cell. Mitochondrial pathology can occur when the level of mutant mtDNA exceeds a given threshold.

What happens to mitochondria with aging? As mentioned above, mitochondrial oxidative phosphorylation is the predominant source of energy in cells, but also the most important source of endogenous free radicals. This led to the concept that the close proximity between the sites of free radical production and mtDNA would render the latter more susceptible to damage than the nuclear genome and lead to defects in mitochondrial metabolism.

It has been reported that mtDNA mutations tend to increase with aging in several tissues of the mammalian body. Such results were first observed in post-mitotic cells such as neurons and muscle cells [21] but have since been described in highly proliferative cells such as the epithelial stem cells of the gut wall [22].

The role of mtDNA in aging is currently under intense debate. It has been found that homozygous knock-in mice expressing a proof-reading-deficient version of the nucleus-encoded catalytic subunit of mtDNA polymerase γ (PolgA) showed an extremely high level of mtDNA mutations and deletions and a significant decrease in lifespan [23]. However, even though mitochondrial function was affected, no evidence for increased oxidative stress was found in these animals [24, 25]. Most strikingly, mice that were heterozygous for PolgA function showed no significant reduction in lifespan despite a mtDNA mutation burden 30 times higher than in old wild-type animals [26]. These studies suggested that mtDNA mutation load does not limit lifespan of wild-type mice and that mtDNA mutations, even at very high levels, do not necessarily lead to increased mitochondrial ROS generation.

These data do not necessarily undermine the involvement of mitochondria in aging. Mitochondrial electron transport chain components are not solely encoded by mtDNA and about 3000 genes participate in the biogenesis of a single mitochondrion (only 1% of these are mtDNA encoded). Thus, it is possible that other factors contribute, together with mtDNA mutations, to failure of mitochondria with aging.

Cell renewal and the telomere loss theory

Another important aspect to take into account when studying cellular aging is the existence of two types of cells in an organism: those which are able to divide and those which cannot divide, the latter called post-mitotic.

As observed for instance in liver, which contains dividing cells, once a partial hepatectomy is conducted, the organ is able to regenerate itself and resume its normal size. The capacity for regeneration may play an important part in delaying the aging process, as dramatically seen in certain organisms such as *Hydra*, which appear to escape senescence by continuously regenerating their cells [27]. Weissman, a German zoologist who was the first to seriously address the problem of aging in the 19th century, obviously thought so and proposed that one of the reasons for aging would be that somatic cells had a finite lifespan [28]. This idea is now again a focus of intense interest in connection with the role played by stem cells in protection against tissue degeneration. A decline in adult stem cell function has been shown

to occur during aging, likely contributing to the decline in organ homeostasis and regeneration with age.

However, most somatic cells (mitotic) do not possess the ability to regenerate indefinitely. As first observed by Hayflick and Moorfield, when fibroblasts are grown in culture they can undergo only a certain number of divisions before becoming irreversibly arrested [29]. Several mechanisms were proposed at the time to explain the phenomenon but none had greater impact than the one first proposed by Russian biologist Alexei Olovnikov. After learning about Hayflick and Moorfield's discovery in the late sixties, Olovnikov predicted that the progressive shortening of the ends of chromosomes (telomeres) might offer an explanation for finite cell division in cells grown in culture [30]. This is a striking example of scientific foresight, since it took more than 20 years to show experimentally that the amount of telomeric DNA declines with aging of human fibroblasts [31] and even more time to show that ectopic expression of the catalytic subunit of telomerase, an enzyme able to counteract telomere shortening, can lead to cell immortalization on its own [32].

Telomere shortening was proposed as a counting mechanism, which could explain two distinct observations: first, the inevitability of the 'Hayflick limit', and second, the fact that one could freeze cells at a certain population doubling (PD) and the cells would retain the memory of their PD and when thawed undergo the expected maximum number of divisions [33]. However, it has also been shown that oxidative stress impacts on telomere shortening and can accelerate the rate of aging of human fibroblasts grown in culture [34], and that alterations in mitochondrial function occurring with aging (including higher production of superoxide radical) could also impact on telomere maintenance [35]. Moreover, population studies have revealed that psychological stress, which is related with higher oxidative stress, could be responsible for the incidence of shorter telomere length in women [36]. This is again proof that the idea of a counting mechanism for telomere shortening only holds true if the influence of both intrinsic and extrinsic sources of stress is excluded.

What is the relevance of telomere shortening to aging? In various cross-sectional studies it has been found that short telomere length (in peripheral blood cells) is associated with an increased risk of various age-related diseases including myocardial infarction, atherosclerosis and Alzheimer's disease [37]. It has also been shown that telomerase-deficient mice, which have very short telomeres, cannot regenerate their liver after partial hepatectomy, suggesting that telomere length has a functional impact on organ regeneration [38]. The same appears to be true for stem cells. Mice with dysfunctional telomeres have decreased proliferation of intestinal stem cells and impaired self-renewal of haematopoietic stem cells, which can be overcome by depleting checkpoint gene p21/Cdkn1a [39].

In summary, several studies have clearly shown that telomeres have a role in stem cell function, organ regeneration and as sensors of stress and therefore play an important role in the aging process. A summary of the main molecular mechanisms involved in the aging process is presented in Figure 2.2.

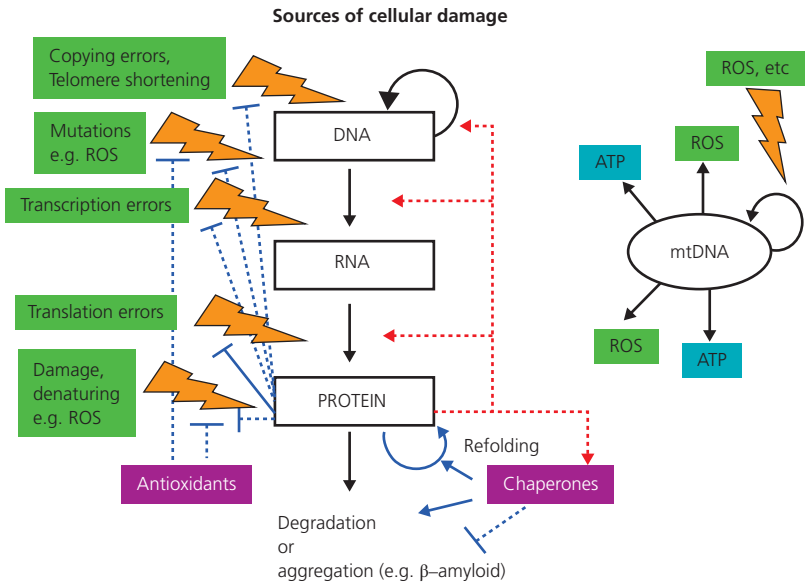

Figure 2.2 Various sources of cellular damage can lead to aging: DNA, RNA and proteins can be subjected to mutations, transcription (RNA) and translation (protein) errors and damage due to increasing reactive oxygen species (ROS) mostly produced by the mitochondria during the aging process. mtDNA can also be affected by the ROS produced by the mitochondria and affect mitochondrial function (including ATP production).

Aging of organ systems

We are now starting to understand the intrinsic processes that lead to the aging of cells, but what is the outcome in terms of tissues and organs? How does aging of cells contribute to organ failure? What major organs are affected with aging?

In the United States in 1900 the three major documented causes of death were respiratory, digestive and central nervous diseases. This had changed dramatically by 1986, when the major causes of reported deaths were cardiovascular complications, cancer and accidents [40]. So, during the 20th century the major causes of death had changed, indicating strongly that changes in the environment had a major impact.

Organ physiology and morphology alter considerably with age. It has been reported that the weight of various organs declines with age, as a consequence of cell loss. Moreover, the amount of fat in the body increases with age and the amount of water decreases. The molecular mechanisms that give rise to these changes are not completely understood. In the next section we will refer to changes occurring in the oral environment with age and also the impact of the immune system on the process. Moreover, we will try to relate these changes to specific molecular mechanisms occurring with aging.

Age-related changes occurring in the oral environment

The primary function of the digestive system is to transform food into a form that cells can use and to provide the uptake of nutrients and excretion of waste. The human mouth, or oral cavity, plays an important role in digestion by providing mechanical maceration of food by teeth. The oral environment also serves as a barrier against infection.

As we have already discussed, recent demographics indicate an unprecedented increase in the number of elderly people. Moreover, more than 66 per cent of older adults now retain their natural dentition, which differs from previous generations. Thus, it is essential to understand the mechanisms involved in the decay in the oral environment that occurs with aging and its consequences.

The teeth and oral mucosa

It is quite difficult to determine if changes occurring in teeth are actually a consequence of age, or a consequence of pathological conditions which can occur early in life and then become aggravated with age. Thus, one can define age-related changes in teeth as changes occurring only in functional, intact teeth from older individuals.

The teeth do change with time due to wear and tear, which leads to changes in the coloration and form of the teeth. The cementum becomes gradually thickened with age. Pulpal changes observed with age include a decrease in the number of cells and increase in the amount of fibrous tissue.

One of the most obvious features of aging is a reduction in size of the pulp chamber, caused by the continual secretion of dentinal matrix (physiological secondary dentinogenesis) by odontoblasts [41].

The specific molecular mechanisms behind tooth decay with aging are not yet known. One possibility is failure of the immune system with aging, to which we will refer later in this chapter. One of the problems occurring in older adults is root tooth decay, mainly due to recession of the gums, which makes the root of the teeth more exposed to bacteria.

Syndromes of accelerated aging have been associated with tooth decay. For instance, Hutchinson–Gilford progeria syndrome (HGPS), which is a rare genetic disorder resulting in phenotypes suggestive of accelerated aging, has been related to the onset of abnormal dentition. Progeria patients are unremarkable at birth, but by two years of age these patients start developing severe growth retardation which results in short stature, osteoporosis, poor muscle development and atrophy and a mean age of death at 12–15 years. The molecular mechanism causing HGPS is the loss of gene encoding for lamin A, which is part of the fibrous network underlying the nuclear envelope. Homozygous mice lacking lamin A show several of the phenotypes commonly observed in HGPS, including abnormal dentition, such as a gap between the two incisors and yellowed teeth [42].

Other mice models of accelerated aging, involving defects in both nuclear [43] and mitochondrial DNA [23], have been associated with loss of bone density and osteoporosis, which can also have an impact on dentition. So, it might be that various molecular mechanisms together contribute to failure of the processes which contribute to maintenance of dentition with age.

Another fundamental process which might influence tooth decay with age is related to age-dependent failure in the teeth's natural ability to regenerate their own damaged structures. It is now well known that teeth possess dental stem cells which are able to produce dentine-like hard structure after injury [44]. Changes in stem cell functionality could interfere with the ability of teeth to repair time-sustained damage.

Salivary glands and secretion

Another important feature of the oral environment is the ability to secrete saliva via the salivary glands. It was once claimed that changes in salivary flow rate are a normal feature of aging. If such claims were true, it would indeed pose an important health issue, since saliva plays an essential