Molecular and Clinical Basics of Gerontology

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# Table of Contents

1. Gerontology ........................................................................................................................................ 1
   1.1. Introduction, definitions .................................................................................................................. 1
   1.2. Population-wide aging ................................................................................................................... 1
   1.3. Chronological and biological age .................................................................................................. 4
   1.4. Etiology of aging: genetic mechanisms and environmental factors .......................................... 4
2. Adaptation and vulnerability, polymorbidity ......................................................................................... 4
   2.1. Progressive deficit in adaptive homeostatic mechanisms in the course of aging .......................... 5
   2.2. Polymorbidity in the elderly ......................................................................................................... 8
3. Nutrition, physical status, body composition, sarcopenia ................................................................. 8
   3.1. Nutrition, physical status, body composition, sarcopenia ........................................................... 8
   3.2. Changes in fat mass (FM) and fat free mass (FFM) with age ......................................................... 10
   3.3. The pathogenesis of sarcopenia .................................................................................................... 11
4. Immobilization, physical activity, disorders of locomotor organs ...................................................... 13
   4.1. The beneficial effects of physical exercise ..................................................................................... 13
   4.2. Immobilation syndrome – chronic bedrest .................................................................................... 14
   4.3. Remobilization in the elderly ....................................................................................................... 18
5. Characteristics of the cardiovascular system, abnormalities and diseases .......................................... 19
   5.1. Age-related alterations in the cardiovascular system ................................................................. 19
6. Changes of the respiratory system, frequent diseases ........................................................................ 23
   6.1. Age-related alterations in the chest and in the lungs .................................................................... 23
   6.2. Age-related alterations in the airways ........................................................................................... 24
   6.3. Abnormalities of other respiratory functions in the elderly ......................................................... 26
   6.4. Diseases of the respiratory system with increased prevalence in old age-groups ....................... 26
7. Changes of renal function, electrolyte/water and acid/base homeostasis ........................................... 27
   7.1. Aging vs. nephron dysfunctions .................................................................................................... 27
   7.2. Aging vs. non-excretory kidney functions ..................................................................................... 31
   7.3. Renal failure in the elderly ............................................................................................................ 31
   7.4. Urinary incontinence in the elderly ............................................................................................... 31
   7.5. Electrolyte and water balance in the elderly ................................................................................ 32
   7.6. Aging vs. pH disturbances ........................................................................................................... 32
8. Changes of the endocrine system and metabolism .............................................................................. 33
   8.1. Age-related alterations in the endocrine system ........................................................................... 33
      8.1.1. Sex hormones ....................................................................................................................... 33
      8.1.2. Synchropause ....................................................................................................................... 33
      8.1.3. The growth hormone (GH), insulin-like growth factor (IGF) system .................................... 34
      8.1.4. Adrenal cortex ..................................................................................................................... 34
      8.1.5. Thyroid gland ....................................................................................................................... 35
   8.2. Functional abnormalities associated with endocrine disorders in the elderly ............................. 35
      8.2.1. Thermoregulation – hot flashes ............................................................................................. 35
      8.2.2. Benign prostate hyperplasia ................................................................................................. 36
      8.2.3. Frailty ................................................................................................................................... 37
   8.3. Age-related alterations in intermediary metabolism ...................................................................... 37
      8.3.1. Carbohydrate metabolism .................................................................................................... 37
      8.3.2. Lipid metabolism ................................................................................................................ 37
      8.3.3. Purine metabolism ................................................................................................................ 37
9. Changes of the gastrointestinal tract, acute and chronic disorders ...................................................... 38
   9.1. Interaction with other systems ....................................................................................................... 38
   9.2. Common disorders in the upper gastrointestinal tract ................................................................. 38
   9.3. Common disorders in the lower gastrointestinal tract .................................................................. 39
10. Neurological and psychological disorders in the elderly .................................................................... 41
   10.1. Age-related alterations of the nervous system ........................................................................... 41
      10.1.1. Stroke .................................................................................................................................. 42
      10.1.2. Neurodegenerative disorders affecting motor functions: Parkinson’s disease .............. 43
      10.1.3. Dementias, Alzheimer’s disease ......................................................................................... 44
## Molecular and Clinical Basics of Gerontology

10.2. Psychological disorders in the elderly ................................................................. 45
   10.2.1. Delirium ................................................................................................. 45
   10.2.2. Affective disorders, depression ............................................................... 45

11. Care of elderly patient ......................................................................................... 46
   11.1. Communication with the elderly patient .................................................... 46
   11.2. Eldercare systems ...................................................................................... 46
   11.3. Polypharmacy (polypragmasia) in the elderly ........................................... 47

12. Successful aging .................................................................................................. 48
   12.1. Factors influencing aging ......................................................................... 49

2. Molecular gerontology .......................................................................................... 52
   1. Basics of molecular gerontology .................................................................... 52
      1.1. Basics ..................................................................................................... 53
   2. Aging theories .................................................................................................. 55
      2.1. Family tree of aging theories .................................................................. 55
      2.2. Evolutionary theories, antagonistic pleiotropy ....................................... 56
      2.3. Programmed theories ........................................................................... 57
      2.4. Damage theories .................................................................................. 58
   3. Mitochondrial aging ......................................................................................... 59
      3.1. Mitochondria are vulnerable .................................................................. 60
      3.2. Mitochondrial damage due to ROS, consequent senescence ................. 62
      3.3. Mitochondrial diseases ......................................................................... 66
   4. Aging and gene expression ............................................................................... 68
      4.1. Telomere shortening .............................................................................. 68
      4.2. Telomere clock of aging ....................................................................... 69
      4.3. Telomerase ........................................................................................... 70
      4.4. Antagonistic pleiotropy ....................................................................... 73
   5. Genetic background of longevity .................................................................... 74
      5.1. Antagonistic pleiotropy and genetic programs ....................................... 74
      5.2. Centenarian studies .............................................................................. 75
      5.3. Longevity genes .................................................................................... 76
   6. Cancer and tumor development, senescence and cancer, epidemiology and statistics .... 82
      6.1. Tumor suppressor genes ...................................................................... 83
      6.2. The ambivalent role of p53 .................................................................. 85
      6.3. Antagonistic pleiotropy and tumor suppressor genes ......................... 87
      6.4. Epidemiology and statistics .................................................................. 88
   7. Alterations of genome due to aging ................................................................. 89
      7.1. Oxidative DNA damage and its repair .................................................... 90
      7.2. DNA damage and its repair in progeria .................................................. 94
   8. Molecular / cellular effects of acute and chronic stress .................................... 98
      8.1. CR extends life-span ............................................................................ 98
      8.2. Reproducibility of CR effects ............................................................... 101
      8.3. CR and antagonistic pleiotropy ............................................................ 101
   9. Metabolism and longevity I .............................................................................. 101
      9.1. Antagonistic pleiotropy ...................................................................... 101
      9.2. Protein peroxidation, repair, associated diseases ............................... 102
      9.3. PUFA controversy ............................................................................... 104
   10. Metabolism and longevity II. .......................................................................... 104
      10.1. Sirtuins as master regulators .............................................................. 105
      10.2. Mammalian sirtuins .......................................................................... 107
      10.3. Functional listing of further mammalian sirtuins .............................. 109
      10.4. Sirt1 mimetic compounds .................................................................. 110
   11. Senescence-related intercellular / intracellular pathologies .......................... 114
      11.1. Lipofuscin or lysosomal waste ............................................................ 117
      11.2. Amyloid aggregates .......................................................................... 118
      11.3. Proteasome function and senescence ................................................... 121
   12. Molecular mechanisms of interventions ....................................................... 127
      12.1. Degree of life-extension, planned interventions .................................... 128
      12.2. Limitations of SENS .......................................................................... 128
   13. Recommended literature ................................................................................. 129
Chapter 1. Gerontology

1. Basics of gerontology, demographic data

1.1. Introduction, definitions

Gerontology (from Greek: Géron = “gray”, “old man”, logos = “study of”) is the study of the biological, psychological and social aspects of normal aging. It is distinct from geriatrics, which is the branch of medicine that studies the characteristic diseases of the elderly or age-related changes in diseases that already began in the young. Biogerontology is a sub-field of gerontology studying the biological processes of aging. It is composed of the interdisciplinary research on the causes, effects and mechanisms of biological aging, in order to achieve better understanding of human senescence. The huge increase in the elderly population in post-industrial Western nations has made biogerontology one of the most rapidly growing fields.

1.2. Population-wide aging

The worldwide prolongation of life expectancy has resulted in a rapid increase in the size of elderly populations (over the age of 65), both in absolute numbers and relative to the whole. Survival has increased with the passage of time since earlier historic periods (epochs) and shows larger improvements in more developed countries. Age-specific mortality has decreased. However, the age maximum ever achieved by human beings has not changed. (Figure I.1-1 and Figure I.1-2)

Figure I.1-1: Survival curves for different populations
Regional differences in mortality or in life expectancy at birth are generally determined by the combination of a huge number of different factors. These differences are known for many regions but are usually compared among nations (Figure I.1-3). One of the very few exceptions is Germany: here the survival conditions are not uniformly distributed over the whole national territory. The East-West differences are due to the special history of these two regions having belonged to completely different political and social regimes for several decades during the last century. The difference remains high despite the political reunion in 1990 (Figure I.1-4).
Figure I.1-3: Expected life-span at birth in different European states
Figure I.1-4: Regional pattern of life expectancy in Germany: East-West difference (2003)

In Europe the number of people over 65 years will increase from 15.5% in 2000 to 24.3% in 2030. These demographic changes have major implications for health care, the labor force, welfare, insurance, and pensions.

1.3. Chronological and biological age

“How old would you feel if you did not know how old you were?”

These two numbers are not necessarily the same. The functional-biological age is determined by physiology rather than chronology. Factors include changes in the physical structure of the body as well as changes in the performance of motor skills and sensory perception.

1.4. Etiology of aging: genetic mechanisms and environmental factors

Aging is a complex process that affects all living organisms. Animals living in the wild are less likely to live long enough to encounter aging, but interestingly all mammalian species (including humans) show similar aging processes if kept under optimal conditions free from external risk factors like predators or famine. The aging process is multi-factorial, and no single factor has been identified which provides a satisfactory explanation of the phenomenon. During the process of aging, the organism accumulates damage to macromolecules of its own cells and tissues and to its organs. The maximum lifespan for humans is around 120 years, whereas the maximum lifespan of a mouse, commonly used in research as a model for aging, is about four years. Genetic differences between humans and mice that may account for these different rates of aging include efficiency of DNA repair, types and quantities of antioxidant enzymes, and different rates of free radical production.

Mutation rate in humans is about 1 per $10^{11}$ base pair. Chromosome abnormalities, demethylation, as well as defects of protein synthesis also influence aging. The acceptable rate of mistakes (faulty aminoacids in the peptide chain) in protein synthesis is about 5/10,000 amino acids. Elongation factor-1 levels are also low in old populations, just as levels of some types of mRNA, e.g. mRNA for IL-1. The telomere is a region of repetitive DNA sequences at the end of chromosomes, which protects the end of the chromosome from damage during cell division. The telomere regions prevent the degradation of genes near the end of chromosomes by allowing for the inevitable shortening of the chromosome, which necessarily occurs during cell division. This telomere shortening mechanism normally allows cell lines only a fixed number of divisions. Animal studies suggest that this mechanism contributes to aging on a cellular level and sets a limit to lifespan. (It has been described that a certain cell type of a certain species is capable of only a certain number of cell divisions: Hayflick phenomenon.) Changing telomere lengths is usually associated with changing rate of senescence. This telomere shortening, however, might be a consequence of, and not a reason for aging.

Maximum lifespan of a species is determined by the rate of aging, inherent in its genes and also by environmental factors, i.e. high metabolic rate, free radical production, excessive caloric intake leading to high serum glucose level.

Further reading


2. Adaptation and vulnerability, polymorbidity
2.1. Progressive deficit in adaptative homeostatic mechanisms in the course of aging

Deficient adaptive functions as well as morphological alterations contribute to age-related disorders observed in aged individuals. Young adults are characterized by maximal performance, maximal reserve capacity, optimal achievement of maximal performance via optimal utilization of capacities/resources. In old age-groups maximal performance of various homeostatic systems decrease to a variable degree due to limited adaptive mechanisms.

Resting physiological normal values of young adults are easy to determine and they show small individual variability. In the course of aging individual variability expands to a great extent, with a small decline in successfully aging individuals and very pronounced falls in enhanced biological aging. Therefore, it is more difficult to determine the “normal range” of parameters of any given homeostatic parameter in older age-groups (Figure I.2-1). Additionally, different homeostatic systems may present different rates of decline within the same individual e.g. prematurely failing vision or graying hair may be observed in people with well-preserved cardio-respiratory fitness.

![Graph showing age-related changes in different functions](image)

Figure I.2-1: Age-related changes in different functions

Although most homeostatic systems may function properly under resting conditions e.g. cardiac output, ventilation, or regulation of serum glucose levels, adaptation to enhanced demands (physical exercise) or to changes in external environmental factors (heat or cold) or those of the internal milieu is very limited (Figure I.2-2, Figure I.2-3).
Figure I.2-2: Effect of 50 mmHg increment in systolic blood pressure on heart rate, cardiac index and stroke index in young and old rats.

In contrast to the maximal performance, maximal reserve capacity, optimal achievement of maximal performance via optimal utilisation of capacities observed in young adults, reserve capacities of old individuals are significantly diminished (Figure I.2-4). Healthy old individuals may well be able to maintain the basic function of vital organ systems, such as the resting cardiac output (CO) of 5 L/min, their capacity to increase the CO in response to physical activity or in a hot or cold environment is very limited. Such limitations of reserve

*50 g glucose p.o.*

Figure I.2-3: Glucose tolerance tests (50 g glucose p.o.) in different age-groups.
capacities make old individuals very vulnerable to environmental stress leading to decompensation of the circulation or to exacerbations of chronic diseases. Limited reserve capacities of numerous organ systems within the same individual will also aggravate complications of diseases, the symptoms of which may be ameliorated by the compensation of other organ systems, e.g. anemic tissue hypoxia will become more severe in old age-groups with limited capacity to maintain a hyperdynamic circulation.

In the elderly, a very delicate balance exists among different organ systems. Disruption of homeostasis by any disease in previously independent, functional elderly persons is likely to be expressed in the most vulnerable, most delicately balanced systems. Therefore, a disease in older persons manifests itself first as functional loss, usually in organ systems unrelated to the locus of illness. For example, it has long been recognized that disorders may present in a masked or apathetic form and inflammatory intra-abdominal disorders such as appendicitis may not evoke typical symptoms and signs. However, it is far less recognized that presenting symptoms in the elderly may be totally misleading with regard to the nature and the primary location of the disease process. For example, when the patient becomes confused, one thinks immediately of psychoactive drugs or disease processes primarily affecting the brain as a possible cause. In an elderly person, one must also consider such diversive factors as dehydration due to a wide variety of etiologies, infection, cardiac disorders, or intra-abdominal organ disease. In short, the diagnostic logic is different.

Geriatrics has described five entities, so-called geriatric giants that are the major categories of impairment appearing in elderly people leading to serious impairment of their quality of life. These include immobility (instability), incompetence (impaired intellect/memory), incontinence, impaired homeostasis, iatrogenic disorders (Figure I.2-5).
2.2. Polymorbidity in the elderly

Polymorbidity and related polypragmasia contribute to the development of iatrogenic disorders. The majority of elderly individuals suffer from a large number of chronic diseases affecting various homeostatic and organ systems. Age-related changes in body composition lead frequently to osteoporosis and sarcopenia, diminished insulin sensitivity in the elderly aggravated by age-dependent accumulation of fat mass frequently culminate in type 2 diabetes mellitus, long-term dust and or smoke-exposure result in chronic obstructive lung diseases or silicosis, progressive atherosclerosis will lead to infarctions or chronic atrophy of the myocardium or stroke, to name just a few. For these diseases and abnormalities old individuals take a large number of drugs regularly.

Further reading


3. Nutrition, physical status, body composition, sarcopenia

3.1. Introduction: age-related changes in body weight and body composition
Aging is accompanied by two major trends in the long-term regulation of energy balance: obesity of the middle-aged and late-appearing anorexia of aging often leading to senile cachexia and sarcopenia. Following a progressive increase in adiposity (Figure I.3-1) first a relative, then an absolute decrease in muscle mass is seen, pointing to the development of sarcopenia (decrease of muscle mass by more than 30%) in aged populations (above the age of 70). At the very end of the aging process adipose tissue is also lost in the process of cachexia. Both of these opposite disorders have enormous impact on the health status and life expectancy of those affected. Not only the consequences of obesity (metabolic syndrome) are serious, but the cachexia of old people as well: it causes muscle weakness, falls, frailty, functional and later cognitive disorders, a higher risk for decubitus (pressure ulcer) and hip fracture, impaired quality of life, a 3-4-fold increase in the risk of loss of self-reliance (expensive assisted living facilities in old age) and higher mortality. They are important especially in Hungary: although the increase in the ratio of the extreme old population is not fast, in the old groups the rate of biological aging is faster, than in more developed countries. Both the weight gain of the middle aged and the sarcopenia of the elderly are multifactorial in their origin (Figure I.3-2).

**Figure I.3-1:** Between the ages of 20 and 70 – despite a stable, normal body weight – body composition is altered: fat mass increases (a 2 fold increase is still considered to be physiological)

**Figure I.3-2:** The pathogenesis and functional vs. metabolic consequences of sarcopenia

\[ GH = \text{growth hormone; } \\
\text{IGF-1} = \text{insulin-like growth factor-1; } \\
BMR = \text{basal metabolic rate; } \\
\text{ADLS} = \text{activities of daily living}\]
3.2. Changes in fat mass (FM) and fat free mass (FFM) with age

Body weight increases gradually by 8.9 kg until 45-55 (this is predominantly an increase in FM with maintained muscle mass), then after a stagnation until the age of 65-75, a decline (1-2 kg/decade) in all tissue types is seen without any apparent cause e.g. a slimming diet. During this period even the FM is decreased somewhat but the loss of muscle mass is dominant. In active athletes the body weight does not increase, the increase of FM with age is blunted (their body fat content is similar to that of young, lean, sedentary individuals). Intensive training decreases abdominal fat. Males have a tendency for visceral fat accumulation, after menopause females too. Fat accumulation does not only mean a simple growth of adipose tissue, but abnormal mesenchymal adipocyte-like default (MAD) cells appear among other cell types e.g. between muscle fibers, in the bone marrow (Figure I.3-3). Redistribution of lipid to extra-adipose sites with aging could result from loss of lipid storage capacity in fat depots (reduced fat cell size and function), altered fatty acid handling resulting in lipid accumulation, maldifferentiation of mesenchymal precursors into a partial adipocyte phenotype (due to falls of testosterone and IGF, elevated cytokine production and anorexia).

The FFM is stable until 40, then it decreases by about 3.5 kg or 3.4%/decade (Figure I.3-4). This change shows small individual differences, the rate of decrease is similar in athletes.
Figure I.3-4: Fat (f), fat-free mass (ffm), and cell mass (cm) of males and females at various ages. (The number of subjects in each age-group is noted.)

The water content of the body changes proportionally with FFM. Water content of the FFM is stable. Bone minerals also change proportionally with FFM. By 65 it decreases by 10-15%. In females the rate of decrease is enhanced after menopause. This dramatic fall can be prevented by estrogen supplementation. In active athletes the rate of decrease is similar, but starts from a higher peak bone mass. Muscle mass and strength diminishes slowly until 50, then the rate is enhanced (sarcopenia). Between 30 and 80 there is a 30-40% decrease also in athletes. Especially the quick, dynamic contractions are impaired. The number of motoneurons/motor units fall. The production of muscle proteins decreases, especially that of type II fibers.

3.3. The pathogenesis of sarcopenia

Weight loss seen in the elderly may be associated to anorexia of aging: between 20-70 years of age the basal metabolic rate decreases by less than 20%, on the other hand daily caloric intake decreases by as much as 35%. In the elderly, the etiology of poor nutrition includes social (such as poverty and isolation), psychological (especially depression) and physical factors (immobilization or missing teeth), abnormal states (heart failure, malignancies, GI abnormalities, chronic inflammation, infections, drugs, etc.). A large number of cases anorexia develops without any apparent reason (real age-related anorexia). The process is similar in all mammals thus the alterations of energy balance may be of regulatory origin (Figure I.3-5). Individual components of the regulatory systems (e.g. transmitters influencing feeding drive or satiety) may change according to different dynamics, that may explain the abnormalities of the energy balance in middle aged people and in the elderly.
Both insufficient and excessive caloric intake exerts negative physiological effects (Figure I.3-6). It has been observed that among middle-aged and old people the severely undernourished persons showed higher mortality rates than the overweight ones. What is more, among the elderly a slight overweight of 10-20% indicated better survival. The higher body mass index among the elderly means a higher amount of muscle mass, that may reach sufficiently high levels to promote survival. To achieve such a higher body weight with acceptable muscle mass a diet relatively richer in proteins and special muscle (strength) training is suggested.
Figure I.3-6: Hypothetical U-shaped curve over the spectrum of caloric intake from insufficient to excessive calories, emphasizing negative physiological effects at both extremes and positive or hormetic effects within a range of normal (regulated) caloric intake

Further reading


4. Immobilization, physical activity, disorders of locomotor organs

4.1. The beneficial effects of physical exercise

In affluent societies the general level of physical activity progressively decreases. This is unfortunate, since physical activity has many advantages regarding physiological functions. It helps to reach or maintain normal, healthy body mass. In active athletes, for example, the usual body weight rise of middle-aged persons is absent. Regular sport improves body composition, it increases the amount of muscle mass (especially the amount of
type-I, slow, red fibers), the ratio of active tissues, attenuates their age-dependent natural loss. Training programs (12 weeks – 3 times a week) may be able to increase the available muscle mass by 10% even in old age-groups. The greater ratio of active tissues enhances the basal metabolic rate. The trained muscle, during prolonged work (longer than 15-20 min) burns fat. On the surface of muscle fibers lipoprotein-lipase appears, which is able to release fatty acids from the circulating lipoproteins. Regular physical activity suppresses the total-cholesterol level, but elevates the serum HDL-cholesterol concentration. Active skeletal muscles are able to take up glucose by an insulin-independent mechanism. Physical activity recruits GLUT 4 glucose transporter molecules to the surface of muscle cells, just as insulin does. Thus, regular activity decreases the insulin requirement, attenuates the strain on β-cells, and helps to prevent type 2 diabetes mellitus. The thermal adaptation capability improves. In working muscles epinephrine induces vasodilation, thereby it decreases total peripheral resistance, therefore regular exercise helps preventing the development of essential hypertension. Regular sports in children and young adults increases peak bone mass by applying traction forces on the bones (piezoelectric effect, activating bone formation). The regular physical activity shifts bone metabolism to greater synthesis even at later ages. Regular sports can help in the prevention of osteoporosis, which would carry the dangers of vertebral compression, pathological fractures, fracture of the hip or the neck of the femur. Physical activity has an effect to decrease stress. It has no negative side-effects, and does not evoke pathological dependence, either. According to human surveys, regular physical activity can attenuate the appearance of depression and dementia, which often develop with advancing age. Data obtained in a mouse-model of experimental Alzheimer disease have shown that appropriate increase of physical activity favorably modifies the level of brain-derived neural growth factor (which is a contributing factor in hippocampal atrophy), and also the amyloid formation. A physically active lifestyle decreases the occurrence of certain cancers (colon, breast, uterus, esophagus, prostate) partly by maintaining normal body weight, partly through humoral factors. It influences insulin sensitivity, the level of insulin-like growth factors and estrogen.

4.2. Immobilization syndrome – chronic bedrest

In the course of some diseases a short-time bed rest has some advantages: this rest decreases the burden of the cardiovascular and respiratory systems. In febrile illnesses as part of sickness behavior, the patients do not have only fever, anorexia, decreased fluid intake, enhanced pain-sensation, lethargy, but they are also feeble and inactive, often somnolent. However, chronic bed-rest is harmful rather than advantageous. Some patients cannot avoid chronic immobilization. Loss of lower limbs, paralysis of the lower half of the body due to transversal lesion of the spinal cord or stroke, coma, extreme weakness, severe pains in the joints and severe chronic diseases (e.g. chronic heart failure, COPD), extreme obesity, rheumatic polymyalgy, hypothyroidism may also lead to immobilization. The incidence and the danger of immobilization are especially high in the elderly.

As many as 1/3 of older persons report yearly a fall or tendency to fall, which is the most common cause of accidents in people over 65 years of age and is the leading cause of mortality due to injury in that age-group. Complications include hip fractures, subdural hematomas and immobility. As a major public health problem, osteoporosis (metabolic bone disorder characterized by a gradual decline in absolute bone mass) also increases susceptibility to fractures especially in the vertebral bodies, the distal radius, and the proximal femur. Bone mass decreases from the age of 55 by around 1%/year in men and by 3-4%/year in women (peak bone mass is reached at 25-35 years of age, its value is higher in men). Inactivity, vitamin D and protein deficiency, hormonal factors (e.g. lower estrogen, secondary hyperparathyroidism, cortisol), alcohol, smoking and certain drugs may accelerate the age-related progressive reduction of bone mass.

Difficulty and unsteadiness in walking, with occasional falls, and stiffness with painful lower limbs are frequently reported by elderly patients and are often related to degenerative joint disease, rheumatoid arthritis or polymyalgia rheumatica. Osteoarthritis is the most common form of joint disease and one of the leading causes of disability in persons above 65 years of age. As a person ages, the water content of the cartilage decreases as a result of a modification of proteoglycan content, thus causing the cartilage to be less resilient. Without the protective effects of the proteoglycans, the collagen fibers of the cartilage can become susceptible to degradation and thus exacerbate the degeneration. Cellular or matrix alterations in cartilage that occur with aging, obesity, trauma, endocrine diseases (e.g. diabetes mellitus) and primary disorders of the joint (e.g. inflammatory arthritis) predispose older persons to osteoarthritis characterized by progressive joint pain, limitation of movement and joint deformity.

Central and peripheral nervous system disorders (late stage of Parkinson disease or neuropathies) may present with motor symptoms. Cardiovascular, respiratory, endocrine, other systemic illnesses, or dementia, depression, isolation, fear of falling, anxiety, with fatigue and lack of motivation for activities of daily living, often limit exercise performance in the elderly, frequently without intrinsic muscle weakness. Drugs, e.g. sedatives,
narcotics (because of sedative effect), diuretics, antihypertensive medication (in the elderly these may cause orthostatic hypotension, dizziness) also enhance the danger of immobilization.

Consequences of a chronic bed-rest depend on the duration and level of inactivity. In prolonged supine position (as in weightlessness) the circulation is rearranged, on the short run the central blood volume increases, the perfusion and hydrostatic pressure decrease in the lower half of the body, the slightly higher preload and stroke volume lead to bradycardia, renal blood flow increases and slight polyuria develops. On the long run (weeks, months), the plasma volume and the efficacy of orthostatic reflexes (regulating blood pressure) decrease. When the patient is mobilized again, the low blood volume is not enough to maintain brain blood flow in an orthostatic position, therefore orthostatic hypotension develops, the patient is dizzy, eventually faints (Figure I.4-1).

![Circulatory adaptation to chronic bed-rest](image)

Figure I.4-1: Circulatory adaptation to chronic bed-rest

Muscle contractures develop (muscles and joints are less moveable). In case if the upper extremities are affected, the elderly patients lose the capability to eat alone, in case of lower extremities one contracture is enough to cause full immobility. A decrease of muscle mass can be observed already on the short-term, but upon a long-term bed-rest it is significantly enhanced. Immobilization greatly enhances the progression of pre-existing osteoporosis in elderly patients. The enhanced excretion of hydroxy-proline is a sign of increased muscle (protein) catabolism, while the Ca-excretion refers to bone absorption. (Figure I.4-2).
The maximal capacity for physical work will not be determined by the capacity of the cardiovascular system (as it normally happens), but by the exhaustion of the muscular system, or lack of local substrates (glycogen). Formation of red blood cells decreases, the low level of total ventilation also lessens the amount of oxygen carried by the arterial blood. The atrophied, deconditioned muscles of poor perfusion take up less oxygen from the blood. The decreased blood volume, decreased muscle tone and mass (decreased filling) and decreased baroreceptor response act to suppress stroke volume. Following chronic bed-rest any physical activity evokes an exaggerated cardiovascular response, e.g. palpitation may appear already at work of low level (and low oxygen consumption). Due to the decreased venous return and hypovolemia the risk for deep venous thrombosis and pulmonary embolism is high. In the elderly population they enhance mortality by about 50%.

The ventilation decreases, the V/Q mismatch becomes pronounced, and the activity of the immune system and the mucociliary clearance of the airways become insufficient. Elderly patients, if bedridden for only a couple of days, may develop congestive pneumonia. Surgical fixation of a fractured neck of femur is indicated mainly by faster mobilization and avoiding the pneumonia mortality induced by long (earlier advised for 9 weeks) bed-rest.

In chronic bed-rest the metabolic rate may be 20% lower than normally. The defense against either heat or cold is weaker. Immobilization decreases intestinal motility. The tendency for constipation increases significantly, even impaction may develop, eventually with consequent fecal incontinence.

The prevalence of pressure ulcer is 30% among elderly patients who are bed-ridden or have to stay in a wheelchair for at least a week. At the points exposed to pressure the skin and the deeper tissues may be damaged in the course of prolonged sitting or lying (Figure I.4-3). Immobilization, fecal-, urinary-incontinence, hypoalbuminemia and shear stress due to the incompetent turning/moving of the patient contribute to the development of pressure ulcers (pressure ulcer staging: Figure I.4-4, Figure I.4-5, Figure I.4-6, Figure I.4-7). Decubitus causes 4-fold increase in the mortality rate of the patients (sepsis).

Figure I.4-2: Urinary loss of calcium and hydroxy-proline during chronic immobilization
Figure I.4-3: Typical points exposed to pressure in immobilization

Figure I.4-4: Stage I of pressure ulcer: lasting erythema on skin surface
4.3. Remobilization in the elderly

Those people who are confined to stay inactive because of an acute disease or are bedridden due to chronic conditions are highly prone to lose their muscle mass and force very quickly. The proportion of the loss can even reach 1.5% per day. The loss is more pronounced in the muscles responsible for sitting up, standing up and standing straight, and therefore, these muscles are essential for everyday life.Gradual mobilization, passive movement and active exercising of joints on a regular basis, proper positioning of patient (prevention of pressure ulcers), replacement of fluids, optimal feeding, regular emptying of bladder, removal of catheter as soon as possible, cleaning of skin and active environment are important therapeutic measures. Certain specialists in geriatric medicine state that one day spent in bed can be compensated by a 2-week workout. Therefore, a personalized exercise program and care must be worked out for every hospitalized, chronically ill patient in order to maintain their physical activity. Maintenance of physical activity as long as possible in the elderly is essential via resistance training and daily activity- and work-oriented special exercises. The ideal frequency, intensity, duration and style of such physical activity have not been fully defined yet. According to the current recommendations, 30-60 min fast walking repeated 3-4 times a week is the most suitable workout during which the pace is slowed down for 5 minutes in every ten minutes.

Further reading
5. Characteristics of the cardiovascular system, abnormalities and diseases

5.1. Age-related alterations in the cardiovascular system

Aging affects the heart and cardiac functions profoundly. The most widespread morphological changes include dilation of the atria, especially that of the left atrium (even in healthy individuals). The structure of the ventricular myocardium exhibits characteristic proliferation of connective tissue, decrease in cardiomyocyte numbers and enlargement of the remaining myocardial cells with decreased contractility and impaired compliance of the ventricles. Depending on the accompanying diseases the ventricles may show overall hypertrophy, maintained mass or dilation with thinner myocardial wall.

The size of the aging heart shows characteristic changes during the cardiac cycle. Under resting conditions the heart of young adults becomes smaller during systole due to a 15-20% shortening of ventricular fibers. Physical exercise induces significantly stronger contraction that results in an even smaller size of the heart at the peak of contraction compared to contractions at rest. No significant end-diastolic dilation of the ventricle is observed in the young (except in cases of extreme strain). The function of the heart at rest is similar in older individuals. However, during moderate physical activity a significant adaptive end-diastolic dilation is observed indicating activation of the Frank-Starling mechanism. Due to the limited contractility, in the elderly it is necessary to increase the end-diastolic volume with consequent pronounced increase in end-diastolic pressure (since the ventricular compliance is reduced) that leads to significant venous stagnation (dyspnea and systemic congestive edema formation in the lower limbs) in older individuals (Figure I.5-1). The end-systolic volume during exercise also exceeds that seen in the young.

Regarding diastolic filling, the early diastolic function (active distension of the ventricles) shows diminishing significance, while late diastolic functions (dependent on atrial contractions) reach higher significance (Figure I.5-2). Functionally, the maximal heart rate acheived by the heart is also diminishing with advancing age (Figure I.5-3). All these alterations in cardiac functions are reflected by the age-related decline both in resting and maximal cardiac output observed in humans (Figure I.5-4). Similar age-related patterns may be observed in maximal oxygen consumption and endurance time during physical exercise, as in healthy individuals, cardiac functions, rather than respiratory ones limit the maximal potential intensity and duration of physical exercise (Figure I.5-5).
Figure 1.5-1: Age-related physiological changes in the heart

- **Young heart**:
  - At rest:
    - Size at the start of heartbeat, at rest: the same as at rest
    - Size at the end of heartbeat, at rest: smaller than at rest
  - During Exercise:
    - Size at the start of heartbeat, at rest: the same as at rest
    - Size at the end of heartbeat, at rest: smaller than at rest

- **Old heart**:
  - At the start of heartbeat, at rest: larger than at rest
  - At the end of heartbeat, at rest: the same as at rest

Figure 1.5-2: Comparison between the early diastolic and atrial contribution to left ventricular filling in persons of a broad age range

- Early diastolic filling volume (% of total filling volume) vs. Age (years)
- Late diastolic filling due to atrial contraction (% of total filling volume) vs. Age (years)

* men * women
Figure I.5-3: Maximal heart rate vs. age

Figure I.5-4: Cardiac output measured at rest and at exhausting exercise (upright position) vs. age
Figure I.5-5: Maximal oxygen consumption and endurance times according to age. (data on trained and non-trained men)

Figure I.5-6: Mean aortic pressure and aortic pulse wave velocity vs. age in rural and urban populations
Age-associated abnormalities of the vascular system also contribute to the decline in cardiovascular functions in the elderly. Atherosclerosis of the small and large vessels grow more progressive with age. As a result, total peripheral vascular resistance increases with age. To this increase, frequent adaptive activation of the sympathetic nervous system also contributes significantly, made necessary (sometimes even at rest) by reduced contractility. The wall of large vessels especially that of the aorta grows progressively rigid and distended. Thus, aortic elastic properties essential in maintaining optimal diastolic flow and pressure become severely impaired. As a result, systolic pressure rises excessively and diastolic pressure drops abnormally (impairing coronary perfusion pressure). Aortic pulse wave velocity increases significantly with age (Figure I.5-6) causing abnormal, harmful wave reflections within the circulatory system impairing coronary blood flow further. Figure I.5-7 summarizes the complex system of cardiac and vascular changes during aging.

Further reading


6. Changes of the respiratory system, frequent diseases

6.1. Age-related alterations in the chest and in the lungs

The lungs (via their large respiratory surface of 70-90 m2) are exposed to damaging effects of the environment all through life. These effects lead to morphological as well as functional abnormalities in the respiratory system.

Mechanics of breathing involve the compliance of the lungs, that of the chest and the activity of respiratory muscles. With age, the elastic recoil of the lungs diminishes due to progressive destruction of elastic fibers and remodeling of the parenchyma induced by inflammatory processes upon prior activation induced by harmful
environmental stimuli and/or age-related mechanisms. Alveolar airspace enlargement is also associated with this process. The chest becomes more rigid at the same time, the respiratory muscles grow weaker from the age of 55 resulting in a progressive increase in the functional residual capacity (the amount of air in the lungs at the end of a normal expiration). Total lung capacity (TLC, the amount of air in the lungs at the end of maximal inspiration) may also increase in healthy old individuals (Figure I.6-1) leading to the development of aging-associated emphysema and barrel chest.

Even more frequently osteoporosis induces the compression of the vertebrae, that enhances the dorsal kyphosis (“dowager’s hump”, Figure I.6-2). Consequent severe reduction of the TLC indicates a restrictive ventilatory disorder in the elderly.

Figure I.6-1: The thorax in the elderly
6.2. Age-related alterations in the airways

Cumulative effects of inflammatory processes activated by noxious agents throughout life induce progressive airway inflammation and an increase in airway resistance that is different from classical chronic obstructive pulmonary diseases (COPD), although the prevalence of the latter also increases in the course of aging. Additionally, age-associated remodeling of the lung parenchyma, reduction of elastic fibers (that are attached to the walls of small airways, anchoring them to neighbouring structures and keeping them from collapsing during expiration) makes small airways increasingly prone for collapse during expiration. Based on these mechanisms, forced expiratory volume in one second (FEV1) shows an age-related decline throughout life (Figure I.6-3). Smoking enhances this decline significantly in susceptible individuals.
6.3. Abnormalities of other respiratory functions in the elderly

Ventilation/perfusion ratio of young adults approaches the optimal value of 1.0. In the elderly, obstruction of small airways with maintained perfusion of hypoventilated alveolar regions enhance dead space ventilation.

Diffusion capacity also declines by about 0.5%/year, due to destruction of interalveolar septa with consequently diminished respiratory surface and fibrosis-induced thickening of the diffusion membrane.

Regulation of respiratory functions also show characteristic age-related alterations. Diminishing responsiveness of the respiratory center to hypercapnia and hypoxia-induced stimuli are thought to be responsible for the small but steady reduction in arterial partial oxygen pressure observed in the course of aging.

6.4. Diseases of the respiratory system with increased prevalence in old age-groups

Due to prolonged exposure to cigarette smoke, to occupational dust and/or gas exposure or age-related suppression in protective antiprotease alpha1-antitrypsin activity, COPD develops with increasing frequency and severity in the elderly. The majority of the patients suffer from chronic bronchitis, a small but significant minority develop different types of emphysema. COPD is currently the 5th most frequent cause of death, but with the present trends it will advance to 3rd place in 15 years.

Bronchial asthma begins typically in children and young adults, but aging induces characteristic changes in this disease group. The previously reversible airway obstruction becomes increasingly irreversible. Thus, the difference between chronic bronchitis and bronchial asthma diminishes with age.

Pneumonias develop with increasing frequency in older individuals due to suppression of immune defence mechanisms in the lungs. The symptoms of pneumonia are not always specific: in the elderly incontinence or confusion may be the dominant sign. A majority (70%) of lethal pneumonias occur in old individuals. Tuberculosis (TBC) also affects the elderly more frequently, even reactivation of long-healed TBC may be observed in old age-groups.

As a result of the above mentioned respiratory disorders, many elderly persons (about 5% of the population above 50 years of age) suffer from chronic respiratory failure.
The highest prevalence of lung tumors is also found in aged populations. In addition to life-long accumulation of the consequences of harmful stimuli, diminished airflow has also been shown to contribute independently to cancer risks.

Aging aggravates various predisposing factors to pulmonary embolism. Immobilisation, visceral obesity, varicose veins, hemoconcentration, polyglobulia induced by chronic hypoxia, etc. increase the risk of deep venous thrombosis and consequent pulmonary embolism. Difficulties in diagnosis make this abnormality one of the frequent causes of death in the elderly.

Further reading


7. Changes of renal function, electrolyte/water and acid/base homeostasis

7.1. Aging vs. nephron dysfunctions

In the elderly renal mass, renal blood flow, the number of functioning nephrons decrease leading to both glomerular and tubular dysfunctions. The glomerular filtration rate (GFR) also decreases progressively with age (Figure I.7-1). By the age of 80, GFR may decrease to 50%, this results in a tendency for azotemia due to fall of kidney perfusion (thirst, heat, cardiac output redistribution e.g. heart failure), but often without proportional rise in serum creatinine level (less muscle lost). In earlier stage of the chronic renal insufficiency the hyperfiltrating nephrons may compensate the hypofiltrating ones and maintain the total GFR at a normal level, but later the hyperfiltrating glomeruli may be destroyed due to high glomerular filtration pressure (Figure I.7-2). The glomeruli become more and more sclerotic, the basement membrane gets thicker (degeneration) leading to proteinuria (even in nonhypertensive, nondiabetic elderly). High protein intake and hyperproteinemia are associated with hyperfiltration and promote progression of glomerulosclerosis.
Figure I.7-1: Age-related reduction in the glomerular filtration rate. Because of the loss of functioning nephrons, the progressive decrease of GFR exceeds that of the renal blood flow.

Figure I.7-2: Age-related changes in single nephron GFR (SNGFR) in % of total nephrons.

The impaired tubular function (decrease in the function of the thick ascending limb of the loop of Henle where the reabsorption of Na-K-Cl without water takes place and impairment of the corticomedullary osmotic concentration gradient, (Figure I.7-3 and Figure I.7-4) leads to hyposthenuria (Figure I.7-5). A disturbance of concentrating ability may be regarded as a defect of water-retention, while a limitation of diluting ability may be regarded as a defect of water-excretion. Limited capacity of either process can cause severe clinical consequences.
Figure I.7-3: Concentration and dilution are interconnected in different segments of the nephron (purple arrows indicate active Na-reabsorption, the green ones the passive water reabsorption)
Figure I.7-4: Changes of osmotic pressure and fluid volume along the nephron. Without ADH, large volume of diluted urine, in case of high ADH levels small volume of concentrated urine is formed. The possible limits of dilution and concentration are determined in the loop of Henle. In case of hyposthenuria (interrupted line), the concentration changes are moderate in the loop, and the renal concentration gradient decreases.

Figure I.7-5: Development of hyposthenuria, isosthenuria: less and less deviation from the specific gravity of the filtrate during both concentration and dilution

Although the ADH production may be maintained or even increased in elderly, in response to ADH the increase in the specific gravity of the urine is diminished due to decreased nephron numbers and dysfunctional receptors (Figure I.7-6). This may lead to water loss and hypertonicity. On the other hand, suppression of ADH is delayed, therefore hypotonicity (hyponatremia) may also develop, e.g. water intake (exceeding the decreased excretion capacity) may lead to “water intoxication”. Tubular effect of aldosterone is also impaired, but there is a tendency for K-loss and hypokalemia due to frequently occurring secondary hyperaldosteronisms in the elderly. Glucose reabsorbing proximal tubular cells still function, therefore glucosuria in old people does not reflect serum glucose level dependably. Decreased kidney perfusion (frequently occurring in elderly e.g. due to circulatory redistribution in heart failure, exsiccosis) and impaired tubular excretion of substances enhance the risk for drug intoxication. The dose of drugs that are eliminated through the kidney has to be decreased.
7.2. Aging vs. non-excretory kidney functions

Defective renal regulation of blood pressure in aged persons enhances the tendency for hypertension (sclerosis of a. renalis and atrophy of renal parenchyma may lead to renovascular and renoparenchymal hypertension), but frequently occurring hypovolemia may cause hypotension. Deficient erythropoietin production (due to reduced renal parenchyma and gonadal hormone secretion) leads to anemia, decreased renal formation of active vitamin D to bone abnormalities (senile osteoporosis).

7.3. Renal failure in the elderly

Besides age-related renal changes (decrease of renal blood flow, GFR, and of ability to concentrate or to dilute urine), diabetes mellitus, hepatic cirrhosis, congestive heart failure, drugs may increase the incidence of acute renal failure induced by acute tubular necrosis in the elderly. Chronic ischemic renal disease and progressive damage of the renal parenchyma lead to chronic renal failure. Diabetes mellitus, hypertension, hyperlipidemia and obesity are the most important risk factors. The most common indication of dialysis due to chronic renal failure is diabetic nephropathy (35-40%). With higher capacity of dialysis, the age-related limits of dialysis have faded away. Among the dialyzed there are less candidates for transplantation due to co-morbidity.

7.4. Urinary incontinence in the elderly

In the elderly, the muscles of the urinary bladder and pelvic floor tend to weaken, the capacity of the bladder reduces which leads to frequent urination. It is often accompanied by incontinence, i.e. involuntary loss of urine. In functional incontinence, the patient is not able to control his bladder due to altered circumstances (e.g. disability, impaired vision, dementia, bigger amount of urine induced by diuretics, diabetes mellitus). Urethral sphincter insufficiency due to weakness of pelvic floor musculature, obesity, prolapsed uterus, atrophic vaginitis, bladder hernia result in involuntary loss of urine upon elevated intra-abdominal pressure (stress incontinence). Overflow incontinence is an unexpected urine loss from the overfilled bladder (urinary retention) e.g. due to benign prostatic hyperplasia, weakness of muscles of the bladder. In cystitis urge incontinence may occur (sudden, unexpected urge to void after certain stimuli). Urinary infections in the elderly often appear with
symptoms of impaired physical and/or mental status. Sepsis can develop quickly and atypically. The treatment of a urosepsis is extremely difficult.

**7.5. Electrolyte and water balance in the elderly**

In elderly persons the spontaneous water intake decreases. Their regulation is insufficient e.g. their thirst sensation is impaired. Following water deprivation fluid replacement is slower and incomplete. (In old animals the angiotensin II-induced water intake is smaller than that seen in young animals. The dypsogenic effect of ADH is weak.) Upon water deprivation or salt and water loss, severe hypovolemia and hypertonicity develops. This can also contribute to the development of orthostatic hypotension in the elderly. Salt/water loss, diuretic therapy, inappropriate excess of ADH (e.g. operation, pain), water intake (exceeding the decreased excretion capacity) cause dangerous hypotonicity. Hypotonicity may lead to cerebral edema, nausea, convulsions, muscle cramps, 6-8 times higher all-cause mortality. On the other hand, upon salt and/or water load a fast elevation of blood pressure can also be observed. Too fast fluid replacement in exsiccosis may result in acute heart failure and pulmonary edema.

Besides age-related changes of renal structure and blood flow, altered responsiveness to hormones plays a role in impaired salt and water balance. The same decrease in plasma volume elicits a smaller RAAS (renin-angiotensin-aldosterone system) activation than in young individuals. The effects of aldosterone, angiotensin, or ADH are diminished compared to those in young adults. Elderly patients cannot properly protect themselves against salt/water overload either. Suppression of baseline RAAS or ADH activity is delayed; activation of natriuretic factors is inefficient (atriopeptin level is high, but effects are blunted).

Overdose of drugs containing potassium, renal failure, cell lysis, use of potassium sparing diuretics in renal failure, side-effect of NSAIDs and hyperaldosteronism are most common causes of hyperkalemia in the elderly. High potassium level results in fatigue, muscle weakness, paresthesias in the lower limbs, metabolic acidosis, changes in the mental status, bradycardia and conduction blocks. Hypokalemia appears usually as a result of insufficient potassium intake, increased loss due to diuresis, vomiting, primary or secondary hyperaldosteronism (e.g. edema). Its clinical signs are muscle weakness, muscle cramps, sleepiness, changes in the mental status, metabolic alkalosis, as a potential complication paralytic ileus or ventricular fibrillation may occur.

**7.6. Aging vs. pH disturbances**

The normal pH value does not change with age, but aging-associated alterations in its regulation may contribute to development of disturbances in acid-base homeostasis. Diabetic ketoacidosis, lactic acidosis, decreased erythropoietin production (anemia), salicylate-toxicosis, diarrhea, renal failure, renal tubular acidosis are the most frequent causes of metabolic acidosis in the elderly. Compensation by hyperventilation is weaker, because of the decreased sensitivity of the respiratory center (for CO2, hypoxia and H+). The aging kidney shows an impaired reaction to acidosis, therefore, it takes longer to normalize pH.

Vomiting, secondary hyperaldosteronism (e.g. chronic congestive heart failure with edema), diuretic-induced hypokalemia and secondary hyperaldosteronism (aggravating already existing secondary hyperaldosteronism of patients with heart failure) may cause metabolic alkalosis in the elderly. Hypokalemia promotes alkalosis by both internal K+-balance (cellular H+/K+ exchange) and external K+-balance (bicarbonate reabsorption in the proximal tubules, in the distal tubules Na+/H+ exchange is emphasized).

Respiratory acidosis may also occur in the elderly. The respiratory center is less sensitive to hypercapnia and to impulses originating from hypoxia (by the age of 70, the sensitivity to hypoxia decreases by 50%, to hypercapnia by 40-50%; arterial pO2 decreases by 0.3% per year). Medications decreasing the sensitivity of the respiratory center, as well as decreased vital capacity and FEV1, decreased chest wall compliance (kyphoscoliosis, obesity), neuromuscular diseases can worsen the respiratory function. Chronic bronchitis is more frequent in older individuals (impaired mucociliary clearance, longer exposition time to environmental pollutants, smoking).

Hypoxia, sepsis, pulmonary embolism, heart failure (enhanced sympathetic tone), liver failure (NH3 accumulation), mild salicylate-toxicosis (regular use of NSAIDs for pain), common situations with anxiety are common causes of respiratory alkalosis in the elderly.

In the elderly mixed acid-base disturbances are also very common. In acute respiratory insufficiency (e.g. pneumonia) combined with heart failure respiratory acidosis is mixed with metabolic acidosis. In serious heart
failure a decreased tissue perfusion leads to lactate (metabolic) acidosis, but diuretic therapy influences the balance towards metabolic alkalosis.

Compensatory capacity of both the kidneys and the lungs is narrowed. In respiratory acidosis, oxygen therapy may be needed. Its danger: due to decreased CO2-sensitivity hypoxia regulates ventilation – oxygen therapy may result in hypoventilation, further CO2 accumulation and CO2 coma. Assisted ventilation may be necessary.

Further reading


8. Changes of the endocrine system and metabolism

8.1. Age-related alterations in the endocrine system

An important role of the aging endocrine system is widely assumed in the background of various age-related alterations, e.g. in body composition, in essential organ functions, in affective disorders of the elderly, etc. (Figure I.8-1). Responsiveness to hypothalamic releasing factors or that of pituitary troph-hormones have been shown to decrease with age. Many hormones have age-dependent normal values. Frequent attempts to use hormone replacement to delay or reverse aging have been made.

8.1.1. Sex hormones

The most spectacular age-related alterations may be observed in the field of sex hormones. Menopause, the sudden decline in estrogen and inhibit levels in females around 50 years of age, that lead to a rise in follicle-stimulating and luteinizing hormones (FSH and LH, respectively) has been associated with hot flashes, osteoporosis, autonomic and emotional dysfunctions. Andropause, the slow and progressive suppression of testosterone may play a role e.g. in the osteoporosis and sarcopenia of the elderly. In males and females alike diminished production of weak androgens, such as dehydroepiandrosterone (DHEA) associated with “adrenopause”, (the failing activity of the adrenal cortex) is likely to contribute to bone resorption and loss of muscle mass/strength. Hormone replacement therapies in the field of sex steroids have been shown to prevent certain age-related dysfunctions and related symptoms.

8.1.2. Synchropause

Healthy, young individuals (humans and mammals) show a characteristic daily pattern called circadian rhythm regarding body temperature, activity, blood pressure (BP), endocrine functions (e.g. release of GH, ACTH, etc.), sleep, etc. In the elderly, such circadian rhythmicity becomes disturbed, most frequently affecting sleep, activity and blood pressure. Disturbances of sleep frequently appear as advanced sleep-phase syndrome (due to an early onset of sleep around 6-8 p.m., the patient wakes up very early in the morning between 3-5 a.m.). Sleep disturbances may lead to non-dipper blood pressure pattern (night-time BP is higher and not lower than the day-time level). In animal studies the otherwise strict circadian rhythm of food intake was also altered (food intake of old rodents was not restricted to the night). Although, the pathogenesis is unknown, decline in melatonin production of the pineal gland is assumed. Low day-time activity, prolonged daily bed-rest may also play a role in the development. Repeated use of sleeping pills may even further aggravate the disorder. Whereas there is no cure for aging-associated disturbances of circadian rhythm, benefits were shown using some therapeutic measures, e.g. bright light therapy in the morning, behavior and chronotherapy (adjusting activity/light and avoiding coffee/nicotine and other stimulation before desired sleeping time), a significantly increased level of
day-time physical activity (e.g. a fitness training program for 3 months) or melatonin administration in the evening.

8.1.3. The growth hormone (GH), insulin-like growth factor (IGF) system

Aging is associated with declines in spontaneous overnight GH-secretion, a reduced GH amplitude and low serum IGF-I levels. Changes in body composition with age are similar to those observed in patients with the adult GH-deficiency syndrome. Administration of GH to the latter group of patients has significantly improved body composition, muscle strength, functional performance and quality of life.

8.1.4. Adrenal cortex

Following the second and third decade of life, there is a continuous decline of adrenal androgen production and the term “adrenopause” has been coined to reflect this.

Adrenal androgens (DHEA and DHEA-S), are the most abundant steroid hormones in the human body, yet we know little about the function of these hormones. Studies utilizing the supplementation of DHEA in autoimmune diseases and Addison's disease provided promising results, demonstrating clear benefits. The issue of replacing DHEA in elderly remains controversial with some reports demonstrating conflicting results. Elderly men with a physiological decline of DHEA did not benefit from DHEA replacement in contrast to women with adrenal failure.

8.1.5. Thyroid gland

Goiter with one or more nodules means the most common endocrine abnormality in the elderly. Its incidence increases proportionally with age. Hyper- or hypothyroidism also occurs more frequently in older populations.

Hyperthyroidism is associated with toxic adenoma or toxic multinodular goiter in iodine-deficient regions, whereas Graves-Basedow disease is the most common form observed in regions with optimal iodine intake. In the elderly, hyperthyroidism does not show those spectacular symptoms characterizing young adults suffering of the disease. No sympathetic hyperactivity is observed, on the other hand, weight loss, weakness, cardiac complications (palpitation, arrhythmias, atrial fibrillation) dominate the clinical picture.

Hypothyroidism is frequently overlooked, its symptoms are often considered to be signs of “age-related decline”. The patients report weakness, somnolence, slow reactions, sensitivity to cold, loss of memory, constipation. Hypercholesterolemia is a frequent finding. Upon diagnosis and treatment, the symptoms are reversible.
Figure I.8-1: Common endocrine alterations in elderly

8.2. Functional abnormalities associated with endocrine disorders in the elderly

8.2.1. Thermoregulation – hot flashes

Young adults show adaptive responses to hot and cold environments, as well. The hypothalamic thermoregulatory centre and the hypothetical set-point (reference value, to which thermoregulatory effectors bring actual deep body temperature closer) show optimal responsiveness (Figure I.8-2). Following menopause the thermoregulatory set-point is destabilized (the normal range appears to be very narrow, compensatory responses, e.g. sweating, flushing are activated too often without physiologically appropriate stimulus). In the background, imbalance of different types of serotonin receptors are assumed (Figure I.8-3).

Figure I.8-2: Premenopausal thermoregulation
8.2.2. Benign prostate hyperplasia

Benign prostate hyperplasia is almost invariably found in older men. It causes significant clinical symptoms in about 25% of the male population. Obstruction of the urethra interferes with the normal flow of urine. It leads to impaired and/or frequent urination, dysuria (painful urination), urinary retention and increases the risk of urinary tract infections. Imbalance of male and female steroids is assumed in the background (Figure I.8-4).
8.2.3. Frailty

Age-related loss of muscle mass/strength and that of bone mass (osteoporosis) lead to weakness, decreased activity, loss of capacity for independent living, pathological fractures. It represents a population-wide health issue. Age-related decline in endocrine functions (e.g. sex steroids, GH and IGF, etc.) as well as low-grade inflammation associated with life-long exposure to toxic and harmful substances, infective agents, metabolic states (acidosis), obesity, genetic factors contribute significantly to these abnormalities (Figure I.8-5).

8.3. Age-related alterations in intermediary metabolism

8.3.1. Carbohydrate metabolism

Diabetes mellitus characterized by an absolute or relative lack of insulin affects around 5-7% of the population. The most common form, type 2 DM typically develops in mature adults above the age of 40. Age-related insulin resistance and impaired glucose utilisation of the tissues contribute significantly to this metabolic disorder of outstanding public health importance (Figure I.2-3, page 27), that leads to potentially lethal acute and debilitating chronic complications.

8.3.2. Lipid metabolism

Dyslipidemia (hypertriglyceridemia, high LDL- and low HDL-cholesterol), one of the criteria of metabolic syndrome promote atherosclerosis, acute myocardial infarction and stroke in the elderly. Diagnosis and treatment are essential for prevention of lethal outcomes.

8.3.3. Purine metabolism

The prevalence of hyperuricemia (accumulation of uric acid, one metabolite of DNA) progressively increases with age, especially in older men. It is also associated with metabolic syndrome. Gout causes acute bouts of painful arthritis, on the long run chronic deformities of joints. Early detection and strict control of blood urate levels have to be achieved, especially in the elderly.

Further reading

9. Changes of the gastrointestinal tract, acute and chronic disorders

9.1. Interaction with other systems

The passage of time is associated with physiologic and pathophysiologic changes in many organ systems, such as the endocrine, the cardiovascular or the nervous system. Those changes affect the gastrointestinal (GI) structure and function. For instance, the elderly may have a decreased ability to raise the cardiac output, which may lead to a decline in GI motility and/or absorption capacity. Altered alimentary functions caused by chronic extraintestinal diseases may also lead to false impressions about the natural process of aging. The prime example is the esophageal motility changes recognized in octogenarians that for decades were assumed to be due to age-determined esophageal muscle changes. Only recently have they been shown to be due to extraintestinal disorders. In fact, research has shown that most age-related alterations in GI motility are results of neurologic rather than muscular changes. Impaired motility may also develop in other regions of the GI tract, e.g. gastric atonia (gastroparesis), constipation, or even paralytic ileus. The intricate interaction between stress and physiologic function is especially pertinent in the aging population. The elderly are subject to not only the usual stresses of adulthood but such additional stresses as loss of family members, friends, and activities at a time of increasing mental and physical limitations and isolation. The interplay of anatomic, motor, and secretory changes often leads to atypical GI symptoms.

9.2. Common disorders in the upper gastrointestinal tract

Dental and oral disorders, xerostomia, dysphagia caused by cerebrovascular accidents or neuromuscular disorders may be associated with malnutrition. Patients with esophageal carcinoma are generally older, and present with rapidly progressive dysphagia and weight loss. Several reports suggest that up to 50% of patients with noncardiac chest pain may have an esophageal cause. Patients with gastroesophageal reflux (GERD) usually have heartburn, but 5-20% may present with only atypical chest pain.

Acid/peptic gastric and duodenal disorders are frequently found in the elderly population. There appears to be a tendency towards a decreasing incidence of duodenal ulcers with age, which may be related to the diminishing gastric acid secretion. Secretory studies have repeatedly demonstrated a decreased acid output with aging and a relative increase in achlorhydria. In association with the decreased acid output, basal serum gastrin concentrations tend to increase with age. Although duodenal ulcer is the predominant form of peptic ulceration in younger individuals, gastric ulcer predominates in the elderly and is much more likely to result in mortality. Gastric ulcers may actually increase in incidence in the elderly, particularly in those who are chronically taking nonsteroidal anti-inflammatory drugs (NSAIDs). These ulcers are usually dangerously silent, since these drugs suppress their major symptoms. In addition, both gastric and duodenal ulcers tend to develop more complications in older patients, such as bleeding and perforation, making surgical considerations more likely. Elderly men occasionally present with upper abdominal pain, often radiating into the back, giant duodenal ulcers. These ulcers, which may exceed 2 cm in diameter, may actually involve most of the surface of the duodenal bulb. Bleeding occurs frequently, and the lesion may involve contiguous organs, such as the pancreas, the gallbladder, or the liver. Stress ulcers are peptic ulcers, usually gastric, resulting from stress. Grossly they are typically small (1-3 mm) and superficial, being limited to the mucosa. Frequently, they are multiple and associated with gastritis. Many predisposing causes include recent serious operations, trauma,
shock, infections, and burns. The important symptom is hemorrhage, which can be massive and life-endangering.

Atrophic gastritis is characterized by increased numbers of inflammatory cells in the stomach wall and variable degrees of atrophy of the gastric mucosa. It is progressive and may eventually develop into gastric atrophy, characterized by a decrease in the number of secretory cells in the mucosa. The diffuse type of gastritis is usually associated with circulating anti-parietal cell antibodies, as well as decreased acid output and elevated serum gastrin levels. It may evolve into into pernicious anemia. It usually presents as a hematologic abnormality in the elderly, with the finding of characteristic achlorhydria with deficient B12 and iron absorption, but the GI symptoms are non-specific. Of major clinical importance is the potential for malignancy of both atrophic gastritis and gastric atrophy, which share the premalignant status of pernicious anemia.

Cancer of various intestinal organs is particularly common in elderly persons, e.g. the incidence of gastric cancer shows a dramatic increase after the age of 60, or the number of colorectal cancer cases are the highest between 65 and 75 years of age.

Figure 1.9-1: The most common gastric disorders in elderly

9.3. Common disorders in the lower gastrointestinal tract

Constipation is a change in bowel motility, with diminished frequency of defecation, often associated with increased difficulty in defecation. In old age, constipation is commonly associated with decreased physical mobility and prolonged transit time (low fiber diet). The so-called terminal reservoir syndrome (constantly distended rectum), is an important cause of overflow fecal incontinence. (It means instances in which the individuals loses stool from the rectum at inappropriate times.) Acute constipation may indicate intestinal obstruction, characterized by a distended abdomen, an empty rectum, vomiting, and fluid levels (niveau formation) seen on upright native abdominal X-ray. Constipation, particularly if associated with intermittent diarrhea, may be a presenting symptom of colon carcinoma. Constipation may also be a symptom of certain systemic diseases (e.g. diabetes mellitus, hypothyroidism, uremia, hypercalcemia, depression, confusion) or a presenting symptom of other diseases of the colon (e.g. diverticular disease). In addition, it may be caused by drugs (e.g. anticholinergics, codeine, aluminium hydroxide or iron).
Fecal incontinence is usually multifactorial. In a number of people the motor unit loss increases with age. It is an idiopathic form and leads to the so-called descending perineum that is associated with loss of the anorectal angle and anal reflex, loss of tone in the external sphincter, and possible rectal prolapse and anorectal incontinence. Diabetes and autonomic neuropathies may produce internal sphincter dysfunction and anorectal incontinence. Neurogenic incontinence usually follows a gastrocolic reflex in a patient with global cerebral disease, e.g. dementia, who is unable to suppress the process of defecation.

Diarrhea of any cause may contribute to symptomatic incontinence, particularly in the elderly, who frequently have decreased sphincteric pressures and continence for liquids compared with younger persons. Fecal impaction is a common cause of diarrhea in the geriatric population; the stool proximal to the obstructing fecal mass becomes liquefied and oozes around the fecalith. Since such patients usually have long-standing constipation and frequent megacolon, they can not sense the movement of stool into the rectal vault and the fecal impaction tonically inhibits the internal anal sphincter, leading to fecal incontinence (paradoxical diarrhea). Age may alter the presentation of malabsorption (major causes: infections, chronic pancreatitis, lactose intolerance, drug side-effects, i.e. long-term and inappropriate use of antibiotics), and chronic diarrhea may affect the aging patient differently and more severely than the young: dehydration and hypovolemia are more severe (especially if the perception of thirst is also impaired), malnutrition.

Diverticulosis, the asymptomatic presence of colonic diverticula (diverticulum is a saclike projection of the mucosa and submucosa through the muscular layer of the bowel), is widespread among older people in Western societies (about 50% of 80-yr-olds). The reason is thought to relate to the fibrous content of the diet: with a low-fiber, low-residue diet being the causative factor. If the colonic content are of low bulk because of a low-residue diet, the shuttling motility required to reverse forward movement is greater and the increased contraction of the circular muscle generates higher pressure within the haustra. This higher pressure, in turn, leads to mucosal herniation through vulnerable points in the colonic wall, where arteries perforate the circular muscle. Since diverticula develop in close proximity to small arteries, bleeding may be one of the presenting symptoms of diverticular disease (other danger: inflammation due to stagnation of diverticulum content).

Vascular diseases of the alimentary canal are extremely rare because of the rich anastomotic circulation, but mortality rate is high. In many cases, if there is a precipitating factor, ischemic colitis may develop. Hypotension producing precipitating factors are e.g. dehydration, hemorrhage, or low-output heart failure. Polycythemia, diabetes, and the use of digitalis are also occasionally precipitating factors.

Age-related changes of the liver are minimal, they are significant only in late stage. The diminished liver mass and blood flow may account for some changes in drug (alcohol) elimination observed in aging patient. Quantitative and qualitative changes are seen in protein synthesis, with an overall increase in intracellular proteins occurs with aging. The accumulation of defective proteins with age may be related to the process of hepatocyte aging. The incidence of cholelithiasis rises with age, and the stones are present at autopsy in about 1/3 of individuals above 70 years of age.

Rapid diagnosis and treatment of medical emergencies in older persons is often impaired because of altered responses to the stress of illness and coexisting medical and environmental problems. In the care of geriatric patients GI bleeding (Figure I.9-2) has a great importance as one of the common gastrointestinal emergency situations (mortality rate approaches 10%). Clinical manifestations are diverse, ranging from change in mental status to syncope or circulatory shock.
10. Neurological and psychological disorders in the elderly

10.1. Age-related alterations of the nervous system

Both the central and the peripheral nervous system show morphological and functional decline with aging. However, individual differences are very significant.

Impaired motor coordination and performance, diminished spatial orientation, slower, uneven gait, weaker postural reflexes, loss of memory, sleep disorders, etc., indicate the decline of the central nervous system.

Peripheral sensory, motor and autonomic deficits indicate age-related impairment of the peripheral nervous system.

Circulation of the brain (cerebral blood flow, CBF) shows some unique characteristics. Although the brain represents a mere 2% of body weight (1.5 kg), it receives 15% of the resting cardiac output, 25% of resting oxygen consumption and utilizes 70% of daily glucose consumption. A remarkable autoregulation of the CBF
may be observed: between 60 and 140/160 mmHg mean arterial pressure (= integrated value of pressure in the arteries), CBF remains stable. Cerebral vessels show different vasomotor regulation from other blood vessels of the body: metabolic products (a rise in CO2, H+, adenosine or K+) cause vasodilation, a drop of CO2, or H+ elicits vasoconstriction. The sympathetic tone fails to induce vasoconstrictor effects here.

Moreover, several special principles are known about the CBF and the intracranial space, such as the Monroe-Kelly doctrine, according to which the cranial compartment is incompressible, any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another. The Roy-Sherrington hypothesis also expresses a similar feature of the CBF. It states that the overall brain perfusion can not increase significantly, local neuronal activity is related to regional changes in both cerebral blood flow and metabolism (1890).

The brain is especially sensitive to ischemia. Because of the lack of energy storage in the brain, a short cessation of blood flow (1-2 sec) leads to loss of consciousness and within 3-5 min irreversible cortical damage develops. The brainstem on the other hand, may tolerate as long as 20-30 min of ischemia. In contrast to other tissues, e.g. to the myocardium, no benefit of ischemic preconditioning (activation of adaptive mechanisms upon short-term ischemia) may be seen in the brain.

Age-related decreases in CBF have been demonstrated in humans as well, as in primates or rodents. This decrease appears to be mainly regional. It affects primarily those regions of the brain (e.g. the limbic system or the association cortex) the functions of which most frequently decline in the course of aging. Density of precapillary arterioles and capillaries decrease. In healthy old rats, the density of arterioles on the cortical surface was almost 40% lower than in young adults. The cerebral vessels also show age-related structural and vasomotor alterations. Autoregulation of CBF is largely maintained in the course of healthy aging, but not in presence of vascular abnormalities. Rigidity of cerebral vessels present enhanced risk for intracranial bleeding in head trauma in old age-groups due to rupture of vessels (e.g. that of bridge veins linking the dura and the brain ruptured upon any strain).

10.1.1. Stroke

The most common neurological disorder of vascular origin affecting the elderly is the stroke. The majority (around 80%) of the cases are ischemic (transient ischemic attacks /TIA/, reversible within 5 minutes to 24 hours, or permanent, progressive stroke), the remaining 20% may be classified as subarachnoidal and intracerebral hemorrhagic stroke. Etiological factors of ischemic and hemorrhagic strokes, e.g. atherosclerosis of large and small cerebral vessels, local thrombosis based on atherosclerotic plaques of intracerebral arteries, embolisation derived frequently from atrial fibrillation or torn away from large atherosclerotic plaques of the carotid or vertebral arteries, systemic circulatory disorders (shock, severe acute heart failure, especially in the presence of age-related impaired cerebral vasomotor responses), and hypertension alone or in association with anticoagulant therapy occur more frequently in the elderly. Early diagnosis and treatment (within 2-12 hours) may save reversibly injured cerebral regions (penumbra) from necrosis (Figure I.10-1), therefore early symptoms (transient weakening of limbs, especially on one side, even slight and transient asymmetry of the face, slight disorders of speech, asymmetry of the tongue, etc.) have to be detected, reported and treated or preventive measures have to be started. Such preventive measures may include sedation, inhibition of glutamate activity, cooling of the head in order to suppress oxygen requirement until neurosurgical intervention or thrombolysis is started. The importance of TIA-s (caused by reversible obstruction of small cerebral vessels) lies in the fact that they indicate a bad general condition of brain circulation and also predict high risk for permanent stroke during the following 2 years.

The complications of stroke are devastating for elderly patients. The result of the usually complex pathomechanism adding bleeding from collateral circulation to ischemic strokes (especially when prior anticoagulant therapy has been started for some other disorder) and ischemia induced by vasoconstrictor substances released from injured tissues in hemorrhagic ones is a widespread damage in the brain. Consequent brain edema leads to increased intracranial pressure (Monroe-Kelly doctrine) and consequent headache, nausea, vomiting, disturbed vision, Cushing reflex (high blood pressure and bradycardia), irregular breathing, confusion, convulsions, even death due to herniation. Additional focal symptoms (disturbances of vision, of speech, dysphagia, sensory /e.g. central pain syndrome/ and motor dysfunctions depending on the site of injury) and especially prominent cognitive dysfunctions affect very badly the quality of life of patients and their families.
10.1.2. Neurodegenerative disorders affecting motor functions: Parkinson’s disease

Among neurodegenerative disorders affecting motor functions Parkinson’s disease is the most common cause of disability above the age of 50 and one of the most frequent disorders of basal ganglia of the brain. Typical symptoms include shaking, rigidity, slowness of movement, lack of facial expression and difficulty with walking. Imbalance of dopamine, glutamate/acetylcholine are assumed in the background (Figure I.10-2). Replacement of dopamine receptor agonists improve symptoms for years, but final decline with extensive pareses and eventual cognitive decline are inevitable.

- Effective and safe – in elderly as well!
- Stroke outcome 30% better

Figure I.10-1: Thrombolysis in stroke
Among other neurological disorders damaging motor functions Huntington-chorea, a neurodegenerative autosomal dominant genetic disorder with abnormal involuntary writhing movements, called chorea and cognitive decline and dementia, Creutzfeldt-Jakob disease, a rare, prion-induced degenerative, invariably fatal brain disorder and myasthenia gravis, an autoimmune neuromuscular disease affecting acetylcholine receptors characterized by progressive fluctuating muscle weakness and fatiguability with pareses and respiratory failure at the end also affect old populations.

10.1.3. Dementias, Alzheimer’s disease

Mental performance of old individuals does not necessarily decline compared to young adults, since certain deficits may be counterbalanced by prior experience and wisdom. Although cognitive activity requiring quick reactions or high degree of precision grows weaker at old age and the speed of processing, working memory, inhibitory functions and memory may diminish, other functions, e.g. wise consideration of circumstances, enhanced analytic capabilities and understanding help to maintain cognitive performance in healthy aging.

Abnormal decline in cognitive functions is defined as dementia (disorders predominantly affecting memory are classified as anamnestic syndromes). Although many factors, such as strokes or silent chronic cerebral ischemia, various neurodegenerative disorders, head trauma, alcoholism or other toxic agents, severe metabolic disorders, deficiency states may facilitate severe cognitive deterioration characterizing dementias, the most common presenile or senile dementia is Alzheimer’s disease.

Alzheimer’s disease is a (premature) progressive age-associated loss of cognitive functions (in middle-aged and older persons) of unknown origin, also involving affective and behavioural disturbances. The incidence rises steeply with age (Figure I.10-3). A minority (20%) of the cases are genetic, 80% are sporadic. Regarding risk factors, age above 65 years, female gender, low education level, positive family anamnesis, head trauma, stroke, alcohol consumption, atrial fibrillation, metabolic syndrome, smoking were shown to increase the probability of disease development. Loss of neurons, synapses and atrophy in the cerebral cortex and certain subcortical regions (e.g. the temporal and parietal lobes, parts of the frontal cortex) are found in the background. Precise pathogenesis is as yet unknown, a number of theories were proposed including the cholinergic theory (reduced synthesis of acetylcholine leads to impaired function), the beta-amyloid theory (dense and insoluble deposits of amyloid beta precursor protein fragments form senile plaques around neurons initiating damage), the tau protein misfolding theory (intracellular neurofibrillary tangles cause microtubules to disintegrate, damaging the transport system of neurons). Additionally, the contribution of inflammation, oxidative stress, accumulation of aluminium in the brain are assumed in the pathogenesis.
No drug has been shown to cure Alzheimer’s disease or delay its progression. Some therapeutic agents that may alleviate symptoms were identified, intensive research is done concerning the efficacy of acetylcholinesterase inhibitors and glutamate NMDA receptor antagonists. Even providing the best care, a safe, emotionally supportive environment, physical exercise and an optimal diet, the average survival is 7 years. The most common causes of death are pressure ulcers and pneumonia.

10.2. Psychological disorders in the elderly

There are no specific syndromes that occur exclusively in the elderly, but any disorder may develop in older individuals.

The most common disorders are delirium, and affective disorders, especially anxiety and depression.

10.2.1. Delirium

Delirium is a clinical syndrome characterized by inattention and acute severe (reversible) cognitive dysfunctions. In young patients only extraordinary abnormalities of homeostasis, e.g. high fever, severe alcohol intoxication, severe metabolic disturbances, drug withdrawal have been shown to cause delirium. In the elderly, functional reserve capacity of the brain declines, therefore many milder disorders may elicit delirium. Prevalence may reach 14 to 56% of all hospitalized elderly patients (more prevalent in men). Postoperative delirium occurs in 15–53% of surgical patients over 65 years, and 70–87% among elderly patients admitted to intensive care units. Risk is increased in a large number of cases due to, e.g. hypovolemia, hypo- or hypertonicity, severe hypoglycemia, sleep deprivation, infections (pneumonia), anemia, in an alarming environment, in chronic renal or hepatic disease, due to immobilization (restraint, catheters), sensory impairment (hearing or vision), in case of special medications (sedative hypnotics, narcotics, anticholinergic drugs, corticosteroids, polypharmacy, alcohol or drug withdrawal), acute stroke, prior history of delirium, meningitis, encephalitis, falls, dementia or cognitive impairment, etc.

10.2.2. Affective disorders, depression

Anxiety and depression are the most common affective disorders occurring in the elderly. Prolonged periods of dysphoria (severe unhappiness) develops more frequently (around 30%) in institutionalized old individuals than in others living with their families (5-10%). These observations suggest that environmental factors, isolation, an environment poor in stimulation, boredom, inevitable physical decline, etc., play a very important role in the etiology. Additionally, age-related alterations in central neurohormonal levels, e.g. enhanced release and efficacy of corticotropin-releasing factor (CRF) may lead to prolonged and enhanced stress, thus it may also contribute to anxiety and depression. Since depression increases the risk for suicide, symptoms and signs have to be looked for, detected and preventive measures (not always medication) have to be implemented.
Further reading


11. Care of elderly patient

11.1. Communication with the elderly patient

In general, basic methods of history-taking and physical examination are not different from that performed by general medicine (e.g. by internists), however, there are differences in geriatric medicine compared to internal medicine. Dealing with elderly patients usually takes longer because during a longer life more diseases are developed (cumulation), due to impaired cognitive functions recalling information is more difficult and slower, lack of proper medical records makes the evaluation of past medical history including diagnoses and surgical interventions more difficult (nowadays this is a rare problem because of the electronic data processing). Patients do not consider certain information important, such as non-prescription drugs, dietary supplements. They regard certain, and often important, symptoms as age-related phenomena i.e. normal part of the aging process. Diseases often present in an atypical manner which makes their assessments even harder. Due to attention deficit and memory loss reporting the data related to the actual complaints can be inaccurate. The accuracy of the anamnestic data and the judgment of the diseases are influenced by the scene: does it take place at home, in a nursery home, outpatient service or in a hospital.

Due to altered pain perception in the elderly, pain assessment also has a special role in geriatric medicine. Elderly patients (although sometimes complain of everything) do not often report pain, they can suffer from severe rheumatologic diseases without having any significant physical or morphological signs, or they can have serious abdominal conditions (i.e. perforated appendix) while experiencing little, if any, pain. This can be very misleading.

From history taker’s view, the thorough history-taking is especially important in order to avoid diagnostic errors and unnecessary examinations. Even repeated sessions involving especially important parts of history taking may be useful. The presence of impaired perception or hearing loss often makes necessary further data gathering including heteroanamnesis. Family members of the old patient are allowed to be present with permission of the patient only. We have to take into consideration the impaired vision, hearing, reduced motor skills of the elderly. Longer time and more patience are usually needed. Patients might notice the lack of patience and they will not reveal important complaints – this can lead to misdiagnoses. We need to list complaints systematically by organs and by order of appearance, and possibly in a casuistic way which is also time-consuming. Written records (kept by the patient or a family member) may be very useful concerning main complaints, symptoms, earlier diseases and list of drugs taken by the patient. Logorrhea should be prevented by asking straightforward questions. It can be important for the patient to see the doctor’s face since mimic motions and lip reading can help to understand the questions asked by the health professional.

Multiple problems of the elderlies require standard and/or systemic structured geriatric assessment. Assessment of mental, physical, functional status (e.g. ability to walk, self-reliance, quantity and quality of diet, activities of daily living, instrumental activities of daily living) and socioeconomic conditions of the patient (i.e. does the patient live alone or in a family or with caregivers, quality of heating, bathroom) are also essential. Decision making involves the evaluation of the interdisciplinary team. Based on comprehensive geriatric assessment, when it is needed, recommendation for long-term senior housing may be issued.

11.2. Eldercare systems
The majority of elderly people live alone or in a household where all members are above 60 years of age. Limitations of everyday activities caused by chronic diseases are typical for 40-50% of the people between the ages of 60 and 69. They affect 60% of men and 72% of women over 70. Thus, more and more people must depend on other persons, relatives, on the social system or on civil organizations. The demand is huge. The supply does not meet the demands. There is a shortage in the number of health care providers, and the lack of a financial background is also obvious.

It must be assessed whether the person is in need to become a resident in a geriatric facility, like a nursing home or other facility providing long-term care. Within the home it should be decided, whether the patient is at the appropriate place. For housing options the followings should be assessed: health needs, social support, cognitive functions, physical abilities – degree of self-reliance, in-home care or continuous supervision is needed. The most important needs in facilities for elderly are certified chief nurse, registered nurses, full-time social workers, therapeutic health professionals, pharmacists, rehabilitation therapists, dentists, nutrition specialists, cleric services, medical services.

Senior day-care facilities are appropriate for the patients who are no longer able to conduct their lifestyle, but their functions are still relatively maintained. Thus, there is no need for them to be monitored continuously. Housing, meal, and limited assistance with hygiene and drug administration are provided. In-home care (home care services) is advantageous for those who would like to stay at home, but they need some kind of assistance temporarily or permanently because of their medical conditions or disability.

More than half of the hospital beds are occupied by patients over 65 years of age. Their activity should be maintained during hospitalization. The aims of therapy in the elderly differ from that in young adult patients. Complete recovery is often impossible. Relief of pain, maintenance or even improvement of physical activity, in functional abilities (better quality of life), self-reliance, independence (feeding, clothing, hygiene, moving) and transition from hospital to (nursing) home are the most important. There is a need for multidisciplinary approach performed by a team.

11.3. Polypharmacy (polypragmasia) in the elderly

The elderly account for 30% of overall prescription drug use, an average nursing home patient would be taking seven types of drugs in average. Side effects of otherwise necessary drugs may impair other functions (anticoagulant treatment prescribed in atrial fibrillation may cause dangerous bleeding in accidents), aggravate other diseases (beta-blockers for hypertension may promote bronchoconstriction in obstructive lung disorders) or they can seriously impair the quality of life of patients (antiandrogenic alpha-reductase inhibitors used in benign prostate hypertrophy may enhance loss of active tissues, muscle weakness, and lead to depressed mood) (Figure I.11-1).

Figure I.11-1: Illness-medication problems to which the elderly susceptible because of their medical problems
Multiple and severe illnesses, poor adherence to medication regimens and altered pharmacokinetics and pharmacodynamics are principal factors in specific therapeutic challenge of drug prescribing for the elderly. 

Aging-associated changes may modify the pharmacokinetics. In less acidic conditions in the stomach NSAIDs can cause more irritations. The longer transition time in the GI system together with the decreased surface of the small intestine and diminished blood perfusion can cause more irritation, delayed absorption as indicated by a smaller and delayed peak plasma level, and decreased first-pass effect after oral administration. Due to a decrease in the albumin concentration (about by 10%) the binding capacity of certain drugs can decrease. In case of simultaneous administration of multiple drugs, the rate of binding to transporter molecules becomes unpredictable while the free fraction of the drug can reach even a toxic level, causing side effects or being involved in drug interactions. Both the total water volume and the distribution volume of water soluble drugs decrease by 10-15%, so their concentration increases by the same percent. Diuretics and insufficient water intake may lead to enhanced (toxic) drug effects (e.g. antiarrhythmic drugs, digoxin, lidocain, theophylline). The amount of the adipose tissue and the distribution volume of lipid soluble drugs increase by about 20% (underdose of e.g. benzodiazepines), in case of an overdose on lipid soluble drugs the elimination process is slower. Very old individuals loose weight and become frail, the proportion of fat decreases so that the volume of distribution for lipophilic drugs again decreases and the serum concentrations increase (risk for overmedication).

Reduced weight of the liver and decrease in hepatic blood flow are often associated with decreased first pass effect and impaired rate of hepatic drug clearance. Due to impaired kidney functions the toxic effects of drugs eliminated via the kidney may increase. Changes of pharmacodynamics in the elderly (blood-brain barrier, receptor properties, homeostatic changes) may result in either increased or decreased responsiveness to certain drugs. Polypragmasy increases the number of side-effects and drug interactions. Above the age of 85 every 5th hospitalization is due to side effects of medication. Simply decreasing the number of drugs may prevent harmful side effects without affecting the quality of life or the life span.

Compliance of the patients decreases with age. Many elderly patients are using a lot of drugs, inappropriately. On the one hand, certain factors depend on the patient. Chronic diseases become more common. Due to the atypical presence of diseases many people use symptomatic treatments. Because of the expectations of both the family and the patient people keep going to see the doctor until they get what they want. The elderly often take over-the-counter drugs about which the doctor is not informed. Due to the uncertain origin of the drugs (from friends, relatives, and commercials), side effects and interactions can appear. On the other hand, there are also factors depending on the physician. An additional drug is given to correct an existing side-effect. Personalized care and the control of drug efficacy are usually missing, multiple parallel drug prescriptions are subscribed by different doctors.

There is no real Evidence Based Medicine in the elderly, since they are not involved in clinical trials. In general, the therapy has to be started using small initial doses and carefully increasing to optimum amounts. In the elderly, quality of life is at least as important as the therapeutic success.

Further reading


12. Successful aging

Aging is inevitably associated with decline and deterioration of strength and adaptive functions. Eventually, it also leads to such organ failures that will result in death. The aim of successful aging cannot be the endless maintenance of youth and optimal performance of the organ systems, but rather a controlled retreat that allow
active enjoyment of life and independent living as long as possible. The main objective is to add life to years instead of prolonging survival at any cost.

12.1. Factors influencing aging

Among the large array of factors influencing aging of the body and mind, moderate caloric restriction and optimal physical activity emerge as the safest and most efficient means to achieve as successful an aging as genes allow.

One widely recognized and safe method of extending maximum lifespan (from nematodes to rodents and humans) is caloric restriction. A 30% reduction in caloric intake of rats increases life expectancy by about 40-50 percent (Figure I.12-1). In Okinawa Island the traditionally low caloric intake may explain longer life expectancy of the inhabitants. There, we find 40 times as many people above the age of 100 than anywhere else in Japan. Moderate caloric restriction diminishes metabolic rate and free radical production to an optimal extent and increases lifespan. Overeating and chronic cold exposure has life-shortening effects via increasing metabolic rate.

![Survival curves for male rats fed ad libitum or restricted to 60%](image)

Figure I.12-1: Survival curves for male rats fed ad libitum or restricted to 60%; a 40% reduction of diet resulted in 48-months survival instead of the normal 30-months

Physical fitness has a number of positive effects on the health and longevity of individuals. It does not only help to maintain a healthy body composition with optimal bone and muscle mass, but it also contributes to the prevention of cognitive decline. Active muscles are able to take up glucose without insulin (enhanced glucose tolerance, improved insulin sensitivity, prevention of type 2 diabetes mellitus). Trained muscles are able to burn fat upon long-term (longer than 15-20 min) low-intensity exercise (prevention of obesity). During training, the number of lipoprotein lipase enzyme copies on the surface of muscle fibers increases. Additionally, in active muscles local metabolites and epinephrine induce vasodilation, decreasing total peripheral resistance (prevention of essential hypertension). Physical training stimulates bone formation. An optimally high peak bone mass developed by the age of 20-25 and slower reduction thereafter are influenced by exercise, it delays the onset of clinically significant osteoporosis. Exercise induces elevations in HDL (“good” cholesterol) and suppresses LDL (atherogenic lipoprotein transporting cholesterol-esters, prevention of atherosclerosis). Physical activity reduces stress without the side effects of alcohol or tranquillisers. Frequent and too high glucocorticoid levels (stress) lead to hippocampus hyperstimulation, and later to loss of memory (s. Alzheimer’s disease in chapt. I.10.). Physical activity even enhances heat tolerance.

Cognitive training and an optimal psychological balance (positive thinking, religious belief) also plays an important role in successful aging at least partly via reduction of anxiety and stress (Figure II.5-10).
The anti-aging industry offers several possible hormonal and other therapies. The evidence for the use of growth hormone as an anti-aging therapy is mixed and based on animal studies. An early study suggested that supplementation of mice with growth hormone increased average life expectancy. Additional animal experiments have suggested that growth hormone may generally act to shorten maximum lifespan; knockout mice lacking the receptor for growth hormone live especially long. Furthermore, mouse models lacking insulin-like growth factor-1 and consequently diminished effects of growth hormone also live especially long. Although growth hormone has positive effects on body composition (increases in muscle and bone mass, reduction in fat accumulation), side-effects include enhanced carcinogenesis, diabetes mellitus, cardiac hypertrophy, etc. Replacement of gonadal steroids, testosterone in older men and estrogen in postmenopausal women reduces a number of age-related disorders including decline in strength, muscle and bone mass with additional inhibition of hot flushes and other postmenopausal symptoms at the price of increasing the risk of cancer, thrombosis, etc. Melatonin levels decline gradually over the lifespan and may be related to lowered sleep efficacy, very often associated with advancing age, as well as to deterioration of circadian rhythms. Melatonin exhibits immunomodulatory properties, and a detrimental remodeling of the immune system is an integral part of aging. Finally, because melatonin is a potent free radical scavenger, its deficiency may result in reduced antioxidant protection in the elderly (especially within the brain). This deficiency may have significance not only for aging per se but it may also contribute to the higher incidence or severity of some age-related diseases. Available data do not allow us to conclude that melatonin has a definite role in extending longevity above normal levels. However, although melatonin cannot be recognized as the 'rejuvenating' agent, some of its actions may be beneficial during the aging process.

Antioxidant food supplements, vitamins or dietary polyphenols may also show beneficial anti-aging properties but their efficacy and significance are limited.
Hormesis is the term for generally-favourable biological responses to low exposures to stressors. Since the basic survival capacity of any biological system depends on its homeostatic ability, biogerontologists proposed that exposing cells and organisms to mild stress should result in the adaptive or hormetic response with various biological benefits. Ideal portions of manageable stress (heat shock – 41°C, exercise, caloric restriction, alcohol, acetaldehyde, irradiation, heavy metals, pro-oxidants, hypergravity) stimulate heat shock proteins (HSP) and as a result, prolong life. Hormetic interventions have also been proposed at the clinical level, with a variety of stimuli, challenges and stressful actions, which aim to increase the dynamic complexity of the biological systems in humans. (However, measuring and grading this type of stress, determining the “optimal” individual dose, age-related modification of doses present difficult problems for specialists.)

In summary, the main preventive objective of anti-aging medicine should be to promote simple beneficial changes in life-style (optimal physical and life activity, moderate caloric restriction, cognitive training, positive thinking) that may improve the quality (and reasonably, also the length) of life without grave side effects or inflicting suffering.

Further reading


Chapter 2. Molecular gerontology

1. Basics of molecular gerontology

Gerontology is the science of aging. Aging is a complex process that affects all living organisms. Aging is not only conceivable in multicellular organisms, but also in unicellular beings, although its meaning is different. Unlike certain diseases that have given morbidity rates, aging is a normal physiological process that affects all creatures with 100% penetration that live long enough to encounter aging. Animals living in the wild are less likely to live long enough to encounter aging, but interestingly all mammalian species (including humans) show very similar aging processes if kept under optimal conditions free from external risk factors like predation or famine. It is of note that among mammalian species there is a nice correlation between body size and mean lifespan (Figure II.1-1).

![Figure II.1-1: Correlation between body mass and lifespan](image)

Already today and increasingly in the future, western developed countries face the problem of aging societies. Due to advances in biomedical research and care, currently a 55 year old person is expected to live up to 85 years of age at death on average in western developed countries. This number is expected to increase further if advances in biomedical research and care increase at current rate and by the year 2030 any 55 year old person is expected to live up to 115 years of age at death on average in western developed countries (according to SENS plans, see corresponding chapter). These plans also calculate with the fact that although morbidity rate occurrence generally increases with age, it appears to peak at the age of 60 years, decelerates after the age of 80 years and practically stalls beyond the age of 110 years (Figure II.1-2).
It is conceivable that this would impose significant economic burden on the pension, insurance and healthcare system if the tendency is expected to continue and function in the current form and setting. Therefore it is an important task to deeply understand the molecular bases of the aging process in order to alleviate economic burden by increasing both average and maximal health-span values within increasing corresponding life-span values. The subject of Molecular Gerontology aims to reveal underlying molecular processes to aid readers interested in biomedical research and care.

1.1. Basics

Let us first describe basic gerontology definitions of life-span values. Average life-span is the age at which 50% of cohort has died. In natural habitats this value is much affected by the environment. Maximum lifespan is essentially the age of the last survivor of the cohort. This largely influenced by genetics along with environmental factors. (Figure II.1-3).

What is lifespan?

- **Average lifespan:**
  Age at which 50% of cohort has died (much controled by environment)

- **Maximum life-span:**
  Essentially the age of the last survivor (much controlled by genetics)
Based on approach there are three major groups of senescence research (Figure II.1-4). One is the biometric branch that considers the mechanisms of aging to be complex and difficult to perform any intervention. Another branch is called inductive, according to this there are few, simple, universal mechanisms that apply and control all aspects of aging. The third major branch focuses on regeneration and renewal, replacement and remodeling.

**Approaches in senescence research**

**Three major branches:**

- **Biometric branch:**
  complex, difficult to perform intervention

- **Inductive branch:**
  few, simple, universal mechanisms

- **Regeneration and renewal branch:**
  focus on replacement and remodeling

Figure II.1-4: Approaches in senescence research

It is inevitable to try to place aging among evolutionary processes. A pioneer of aging research, August Weismann has established two rather opposing concepts for aging and even today both gather numerous followers (Figure II.1-6). One is the adaptive concept, according to which aging has evolved to cleanse the population from old, non-reproductive consumers. The other, non-adaptive concept suggests that aging is due to greater weight on early survival / reproduction rather than vigor at later ages. This latter has been fine tuned by the theory of antagonistic pleiotropy discussed in detail with examples in several chapters. The science of aging has already attracted much focus (Figure II.1-6) and will likely gain even more and we hope that readers find current and novel findings equally interesting as the editors of this booklet.

**August Weismann’s concepts on aging**

- **Adaptive concept:**
  Aging evolved to cleanse the population from old, non-reproductive consumers

- **Non-adaptive concept:**
  Aging is due to greater weight on early survival / reproduction rather than vigor at later ages

Figure II.1-5: August Weismann’s concepts on aging
Pioneers of aging research include

- Denham Harman
- George Sacher
- Nathan Shock
- Bernard Strehler
- Alex Comfort
- John Maynard Smith
- Zhores Medvedev
- Paola Timiras
- Loenard Hayflick
- George Martin

Figure II.1-6: Pioneers of aging research include

2. Aging theories

During the past decades numerous aging theories have emerged (Figure II.2-1). This chapter will enumerate the major theories and concepts, however without going into detailed description due to space limitations.

Figure II.2-1: The family tree of aging theories

2.1. Family tree of aging theories

There are numerous aging theories that may be categorized into groups (Figure II.2-2). The major groups of aging theories include evolutionary theories, programmed theories, damage theories and one that goes beyond molecular biology (Figure II.2-3).
Major groups of aging theories

- Evolutionary theories
- Programmed theories
- Damage theories
  - General formulations
  - Individual mechanisms
  - Stress induced premature senescence (SIPS)
- Beyond molecular biology of aging

2.2. Evolutionary theories, antagonistic pleiotropy

Evolutionary theories include programmed death theory, mutation accumulation theory and antagonistic pleiotropy theory (Figure II.2-4).
Evolutionary theories of living and longevity

- Programmed death theory
- Mutation accumulation theory
- The antagonistic pleiotropy theory

Programmed death refers to the presence of a genetic program that artificially limits maximal life-span and dictates the pace of aging due to genetically encoded processes. The mutation accumulation theory places emphasis on genomic stability and its maintenance. Once genomic instability is reached due to exceeding the threshold level of accumulating mutations, mass apoptosis occurs due to irreversible loss of genotypic and phenotypic integrity. Antagonistic pleiotropy is an elegant theory that describes trade-offs between two opposing strategies of species sustenance (Figure II.2-5).

Theory of antagonistic pleiotropy

- Trade-off between fertility and longevity genes
- Optimal conditions: invest in growth and reproduction
- Restrictive conditions: shut off reproduction, invest in somatic maintenance and survival

One places emphasis on quick development and rapid reproduction without investing resources in long-term maintenance of genomic integrity, long-lasting health or cancer-prevention. The other is the opposite with slower developmental rate, slow reproduction and emphasis on long-term maintenance of genomic integrity, long-lasting health or cancer-prevention. Interestingly, calorie restriction, the currently only known, widely accepted form of life-span extension switches from the former to the latter, mainly via sirtuins, as discussed in subsequent chapters.

2.3. Programmed theories
Programmed theories of aging place emphasis on one of the following: the immune system, the neuronal system or various clock machines (Figure II.2-6). It is logical to highlight the role of the immune system as it distinguishes between self and non-self structures thus maintaining integrity as long as possible despite attacks at all levels. The neural system is also of key importance in the survival of most multicellular animal species and one can reason that once mental control is lost over the body, life soon ceases due to predation or famine. The existence of external clock machines has long been suggested. There is ample evidence that supports telomere length being an indicator of cellular age at the molecular level discussed in detail in the chapter dealing with telomeres. Others argue for the existence of a hormonal pacemaker machinery to set the pace of aging. Indeed, hormonal and circadian systems significantly overlap in support of the theory.

**Programmed theories**

- Immune system compromise
- Neurological degeneration
- Hormonal theory of aging
- The genetic clock
  *(programmed epigenomic theory)*

Figure II.2-6: Programmed theories

### 2.4. Damage theories

Damage theories enumerate both general formulations and individual mechanisms (Figure II.2-7 and Figure II.2-8). General formulations include the theories of misrepair accumulation, waste accumulation, error catastrophe as well as wear and tear. Individual mechanisms that can affect the pace of aging rate include chronic or excess inflammation, mitochondrial damage, methylation, glycation, oxidative damage via ROS and somatic DNA damage via mutations.
It is most likely that there is no uniform theory of aging that can describe all possible aspects of aging, but rather aging is a complex process and hence all the theories described above have relevance for those interested in modeling senescence.

3. Mitochondrial aging

The mitochondrion is a very unique cellular organelle. It is the powerhouse of eukaryotic cells. Various tissues possess different numbers of mitochondria depending on the energy requirement. Mitochondria are also the major sources and targets of ROS. In fact these organelles show rather dynamic life as they undergo budding, fission and fusion processes (Figure II.3-1). Mitochondria exhibit maternal inheritance through the oocyte
demonstrated by mitochondrial diseases accumulating in males. Mitochondria are rather odd cellular organelles as they share prokaryotic evolutionary roots in an eukaryotic environment. Mitochondrial DNA is double stranded closed circular DNA of 16,569 bases. It encodes 37 genes, 2 rRNAs, and 13 respiratory chain polypeptides.

**Characteristics of mitochondria and mtDNA**

- Various number and size, dynamic structures (budding, fusion, fission)
- High metabolic activity, intracellular powerhouse, major source and target of ROS
- Extraneuronal, double stranded, closed, circular mtDNA, its length is 16,569 bp
- mtDNA Encodes 37 genes, 2 rRNAs, 22 tRNAs, 13 respiratory chain polypeptides

Figure II.3-1: Characteristics of mitochondria and mtDNA

**3.1. Mitochondria are vulnerable**

Mitochondria are vulnerable organelles. They undergo proliferation processes independent from genomic DNA (Figure II.3-2), yet they are more susceptible to suffer stable genetic variations. Mitochondrial DNA is extremely economical, there are no introns and only minimal non-coding DNA (Figure II.3-3). Mitochondrial DNA is not protected by histones, resident repair mechanisms are less efficient and damages are very likely to affect coding regions. As a consequence mitochondrial DNA is approx. 10 times more prone to suffer stable genetic variations than genomic DNA on the same time-scale (Figure II.3-4).
Initiation factors
- RNA Polymerase
- mtTFA
- mtTFB1
- mtTFB2

Additional activities
- Priming
- RNaseH1/5'→3' Exonuclease
- Ligase III

Figure II.3-2: Mitochondrial DNA replication fork

Figure II.3-3: Genes encoded by mtDNA
Reasons of mitochondrial vulnerability

- Extreme economy of coding sequences (minimal non-coding DNA, no intron)
- Not protected by histones
- mtDNA repair mechanisms are less efficient
- mtDNA mutation rate is 10× greater than gDNA

3.2. Mitochondrial damage due to ROS, consequent senescence

The free radical theory of aging was first assumed by Denham Harman in 1972 (Figure II.3-5). ROS (reactive oxygen species) are molecules with unpaired electrons, by-products of the respiratory chain event.

Reason and evidence of mitochondrial aging

- Superoxide (ROS) leak is 0.1% in mitochondria
- SOD and co-enzyme Q levels affect life-span
- Cardiolipin level decreases with age

As a consequence, approx. 90% of ROS are produced by the mitochondria. Superoxide (a major ROS type) leak is approx. 0.1% in active mitochondria posing deleterious, irreversible effects on neighboring mitochondrial macromolecules (Figure II.3-6, Figure II.3-5, Figure II.3-7 and Figure II.3-8).
ROS and their major sources

- Theory of Denham Harman in 1972
- Molecule with unpaired electron
- Mitochondrial respiratory chain leakage (90%)
- Dopamine, nor-epinephrine
- NOS (nitric oxide synthase)
- Respiratory bursts of leukocytes
- Environmental stimuli causing redox disbalance

Figure II.3-6: ROS and their major sources

Mitochondrial oxygen radical theory of aging (fulfilment of major aging theory criteria)

- ROS production is endogenous
- Continuous effect, changes progressive with age
- Deleterious effects on mtDNA
- Irreversible effects

Figure II.3-7: Mitochondrial oxygen radical theory of aging
Enzymatic activity capable of blocking superoxide damage (i.e. SOD and coenzyme Q) shows very tight correlation with life-span. The list of antioxidants (molecules counter-acting ROS) is long and includes SOD types (CuZnSOD, MnSOD, FeSOD), catalase, glutathione peroxidase, vitamins C, E, carotenoids, GSH (glutathione) and uric acid (Figure II.3-9). Cardiolipin, a major mitochondrial component that is often targeted by autoimmune diseases shows decreasing level at increased ages. Complex I of the respiratory chain is the major source and target of ROS production (Figure II.3-10). Interestingly, calorie restriction, the most acknowledged intervention known to increase life-span targets complex I as well.
**Antioxidants**

- SOD (CuZnSOD, MnSOD, FeSOD)
- Catalase
- Glutathione peroxidase
- Vitamins C, E
- Carotenoids
- Coenzyme Q10
- Glutathione (GSH)
- Uric acid

Figure II.3-9: Antioxidants

**Mitochondrial ROS production**

- Mitochondrial ROS production is relevant parameter of aging
- Anti-oxidants are usually not rate-limiting
- Issues of CuZnSOD/MnSOD/FeSOD, GSH-peroxidase
- Complex I of respiratory chain is main target and source of aging rate
- Caloric restriction targets complex I as well

Figure II.3-10: Mitochondrial ROS production
A good marker of mitochondrial oxidative damage is 8-oxoDG. This molecule is not only a good marker, but a strong mutagenic factor (Figure II.3-11). Of note, calorie restriction targets 8-oxoDG levels too.

**mtDNA oxidative damage**

- Marker for oxidative mtDNA damage: 8-oxodG
- 8-oxodG level is 10x > in mtDNA than in gDNA
- Inefficient repair of 8-oxodG mtDNA damage
- 8-oxodG alone is also mutagenic
- Calorie restriction targets 8-oxodG levels as well

Figure II.3-11: mtDNA oxidative damage

### 3.3. Mitochondrial diseases

The extent of mitochondrial damage (i.e. cytochrome c oxidase or COX deficiency) shows high correlation with the frequency of morbidity (i.e. hospital admissions) (Figure II.3-12, Figure II.3-13). Organs / tissues most aggressively attacked by mitochondrial diseases share extreme energy turnover: nervous system, heart, skeletal muscles, intestines, liver, kidneys, pancreas (Figure II.3-14, Figure II.3-15). It is of note that the very same polymorphisms may also be related with diseases and longevity. Due to mitochondrial redundancy, no symptom develops until mitochondrial mutation rate exceeds 60% (Figure II.3-16). Interestingly, clonal expansion of mutant mitochondria may often occur as mutant mitochondria function less efficiently producing less ROS (and energy) thus also showing extended life-span compared to wild-type mitochondria that function and suffer damages and normal rate.

Figure II.3-12: mtDNA damage and hospital admission
Figure II.3-13: Mitochondrial apoptosis due to ex. stimulus

Figure II.3-14: Organ / tissue specific diseases of mt origin

**Nervous system:**
Seizures, spasms, developmental delays, deafness, dementia, stroke (often before age 40), visual system defects, poor balance, problems with peripheral nerves

**Skeletal muscle:**
Muscle weakness, exercise intolerance, cramps, excretion of muscle protein/ myoglobin in urine (myoglobinuria)

**Liver:**
Liver failure (uncommon except in babies with mtDNA depletion syndrome), fatty liver (hepatic steatosis)

**Digestive tract:**
Difficult swallowing, vomiting, feeling of being full, chronic diarrhea, symptoms of intestinal obstruction

**Eyes:**
Drooping eyelids (ptosis), inability to move eyes (external ophthalmoplegia), blindness (retinitis pigmentosa, optic atrophy), cataracts

**Heart:**
Cardiomyopathy (cardiac muscle weakness), conduction block

**Pancreas:**
Diabetes

**Kidneys:**
Falcioni’s syndrome (loss of essential metabolites in urine), nephrotic syndrome (uncommon except for infants with coenzyme Q10 deficiency)
Aging and gene expression

4. Aging and gene expression

Aging affects gene expression at multiple levels. Once genetic material aging reaches a certain threshold level gene expression completely shuts down. This is often achieved due to telomere shortening.

4.1. Telomere shortening

Telomeres are chromosomal DNA ends that fulfill the function of chromosome capping (terminal loop) and stabilization. Telomere sequence is made up of over 1000 repeats of the sequence: TTAGGG (Figure I.1-4). Telomere shortening occurs during replication due to the problem of end-replication. DNA polymerases depend on primers and miniature but detectable shortening occurs with every replication round due to primer annealing characteristics. This cumulative shortening exceeds a destabilization threshold beyond which chromosomes

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</table>
suffer structural damage and break up. In the case of human cells this threshold is usually achieved following 30-50 divisions ex vivo. It is of note that telomere loss rate is not stable, increased oxidative stress also increases telomere shortening rate resulting in premature loss of telomere capping (Figure II.4-2).

### Telomeres as biological clocks

- Most favored clock, but cause or marker?
- Sequence: TTAGGG hexanucleotide > 1000×
- Polymerase leaves gap with every replication
- Oxidative stress accelerates telomere loss rate

Figure II.4-1: Telomeres as biological clocks

### Factors influencing telomere loss rate

- Telomeres form terminal loops for stability
- Role of TRF2 in telomere stability
- Issue of telomere length threshold
- Issue of telomere loss rate vs. stress rate

Figure II.4-2: Factors influencing telomere loss rate

### 4.2. Telomere clock of aging

Telomere shortening has been described to occur in most organisms, although initial telomere length at birth is species-specific just like the tissue / cell expression pattern of telomerase activity. For example mice have much longer telomeres compared to humans and also telomerase activity is more widespread among various tissues and cells in contrast to humans. As a consequence, telomere shortening is an insignificant problem in mouse cells compared to human cells.
Nevertheless telomeres are often referred to as the molecular level ticking clocks of aging (Figure II.4-3). This assumption is tempting as telomeres indeed become shorter with increasing numbers of cell divisions and can therefore be regarded as counters. However, further studies are required to correlate telomere length and molecular level age indicators to clarify whether telomere shortening is the cause or the result of aging.

Further clocks ticking

- Soluble factors / cell non-autonomous spreading
- Pineal clock, role of melatonin
- Circadian clock mechanisms
- DNA methylation, acetylation, de-acetylation

Figure II.4-3: Further clocks ticking

4.3. Telomerase

Telomere loss rate can be slowed down and even reversed. As oxidative stress can increase telomere loss rate, all mechanisms that help to minimize oxidative burden on genomic DNA also minimizes telomere loss rate. The most acknowledged mechanism to increase telomere length is via telomerase activity (Figure II.4-4). Telomerase enzyme can efficiently increase telomere length pushing the threshold limit increasingly distant in cells with telomerase activity. In humans under normal conditions only few cells express telomerase including stem cells and germ cells. However, telomerase activity can be up-regulated in practically any kind of cell as confirmed by various cancer cells that reach final immortality this way (Figure II.4-5, Figure II.4-6), (Figure II.4-7, Figure II.4-8). ALT or alternative telomere lengthening is a poorly characterized process during which telomere length increases via a telomerase-independent mechanism (Figure II.4-9).
Figure II.4-4: Telomere sequence and telomerase function

Figure II.4-5: Changes in telomere length

Figure II.4-6: Significance of telomere in cancer
Figure II.4-7: Cancer development and telomeres

Figure II.4-8: Acquiring immortality via telomerase
**Slowing, reversing telomere shortening**

- Counteracting (oxidative) stress conditions
- Telomerase activity increases telomere length
- ALT: alternative telomere lengthening

Figure II.4-9: Slowing, reversing telomere shortening

### 4.4. Antagonistic pleiotropy

As discussed above, mice and humans have dissimilar telomere length strategies. This is due to the reason that mice are short lived and invest energy into rapid maturation and breeding, while humans in contrast are long-lived and invest energy into long-term genome maintenance and control over cancers. This trade-off is a classical representation of the antagonistic pleiotropy theory of the evolutionary aging model (Figure II.4-10, Figure II.4-11).

**Antagonistic pleiotropy: telomere length I**

- Mouse telomeres are extremely long
- Mouse tissues often express telomerase
- Mouse cultured cells ‘spontaneously immortalize’
- Human telomeres are much shorter
- Most human tissues lack telomerase
- Human cultured cell immortalization is zero

Figure II.4-10: Antagonistic pleiotropy – telomere length I
Antagonistic pleiotropy: telomere length II

- **Rodent strategy:**
  high annual mortality, low chances of cancer development = long telomeres, active telomerase to fight ROS

- **Primate strategy:**
  low annual mortality, elevated chances of tumors = short telomeres, lack of telomerase to fight cancer

Figure II.4-11: Antagonistic pleiotropy – telomere length II

5. Genetic background of longevity

There is a positive correlation among animals, especially mammalian species, between body size and life-span. (Figure II.5-1). Life-span, especially maximal life-span is significantly affected by the genetic set of individuals and hence it is sensible to investigate for longevity assurance genes.

![Graph showing correlation between body mass and lifespan](image)

Figure II.5-1: Correlation between body mass and lifespan

5.1. Antagonistic pleiotropy and genetic programs

Longevity is one of the major genetic programs encoded in complex animals including mammals and many theories have been created on longevity / aging (Figure II.5-2). Depending on the easy accessibility of nutrients and relative protection from predation the longevity program is switched on or off. Following the trade-off rules of antagonistic pleiotropy in times of unlimited food access emphasis is put on rapid growth and reproduction (Figure II.5-3). However, if nutrient accessibility is significantly decreased the genetic program providing longevity and somatic maintenance is turned on. It is suggested that calorie restriction, the most acknowledged
life-extending intervention operates the same way turning on the Sirtuin switch that diverts metabolism and extends life-span.

![The family tree of aging theories](image1.png)

**Theory of antagonistic pleiotropy**

- **Trade-off between fertility and longevity genes**
- **Optimal conditions:** invest in growth and reproduction
- **Restrictive conditions:** shut off reproduction, invest in somatic maintenance and survival

![Theory of antagonistic pleiotropy](image2.png)

**5.2. Centenarian studies**

Several studies have been performed with healthy centenarians comparing their genetic make-up and various physiological parameters with the rest of the population. Statistics reveal that human morbidity peaks at 60 years of age, decelerates after 80 years of age and remains practically linear after 110 years of age (Figure II.5-4, ). Centenarians may be divided into three categories depending of how they managed to live that long: survivors, delayers and escapers. Survivors do have a chronic disease with which they have lived for more than 20 years (~40%). Delayers develop diseases later, beyond the age of 80 years (~40%). The rest is called escapers being practically healthy at the age of 100 years. Studies also reveal to what extent genetics and the environmental conditions affect actual life-span. It is estimated that genetics has the most effect (~40%), while environmental conditions and pure luck have equally strong effect (~30% each) on individual life-span.
Centenarians

- Morbidity rate increase peaks at 60y, decelerates after 80y, remains linear after 110y
- Environmental effects are strong: centenarians’ spouses gain >15 years over controls
- Three major categories of extreme longevity: survivors, delayers, escapers
- Average lifespan: 30% genes, 40% environment, 30% pure luck

Figure II.5-4: Centenarians

![Graph showing morbidity rates and age](image)

Figure II.5-5: Correlation of morbidity rates and age

5.3. Longevity genes

The balance of aging is a complex process and beyond metabolism-related genes there are many others like DNA stability and repair genes involved in defining maximal life-span (Figure II.5-6, Figure II.5-7, Figure II.5-8 and Figure II.5-9). Following the analysis of longevity genes it has been found that these have been conserved during evolution (Figure II.5-10, Figure II.5-11). It has been demonstrated that poly (ADP-ribose) polymerase (APRP) activity directly correlates with lifespan across mammalian species. The XPF-ERCCI endonuclease can
also have progeroid mutations affecting secondary and tertiary DNA structures. Sirtuins have been shown to influence metabolism, but also deacetylate p53 thus affecting cell survival and life-span of the organism.

Figure II.5-6: Molecular balance of aging and life-span

Figure II.5-7: Connection of metabolism and longevity
Figure II.5-8: Molecular pathways of aging and life-span

**Genes influencing longevity I**

- DNA stability and repair genes
  - Poly(ADP-ribose) polymerase (PARP) activity directly correlates with life-span
  - XPF-ERCC1 endonuclease, progeriod mutations, secondary and tertiary DNA structures
  - Sirtuins deacetylate key proteins including p53 and show direct correlation with metabolism

Figure II.5-9: Genes influencing longevity I
### Genes affecting age-related diseases

- Apolipoprotein E, frequency of ApoE-e4 allele is very low among centenarians
- Cholesterol ester transferase protein, affects HDL and LDL particle size
- Apolipoprotein C, ApoC3 promoter CC polymorphism accumulates in centenarians
- Microsomal transfer protein (MTP) 493 G6'T variant is rare in aged
- Prolyl isomerase (PIN1) protein folding chaperone genetic variations affect Alzheimer's frequency

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**Table:**

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<td>Insulin-like receptor (glucose metabolism)</td>
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<td>daf-16</td>
<td>HNF3 (transcription factor)</td>
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<td>WRN</td>
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**Figure II.5-10:** Longevity genes across animal kingdom

**Figure II.5-11:** Genes affecting age-related diseases

Reactive oxygen species (ROS) cause macromolecular damage that significantly affects expected life-span and hence factors influencing ROS production and protection from ROS effects are equally important in defining life-span (Figure II.5-12). It has been shown that p66Shc (SHC1) deletions increase ROS resistance and increase life-span, paraoxonase 1 (PON1) protects LDL from oxidative damage and has key function in atherosclerosis, Klotho (KL) gluturonidase influences coronary artery disease frequency, superoxide dismutase (SOD) and
catalase (CAT) affect ROS capture and thus alter life-span, and finally the hemochromatosis gene (HFE) also modifies ROS damage via the Fenton reaction and may fine-tune expected life-span.

Genes influencing longevity II

- Defense against ROS
  - p66Shc (SHC1) signal transduction of oxidative stress, deletions increase ROS resistance and life-span
  - Paraoxonase 1 (PON1) protects LDL from oxidative damage, key in atherosclerosis
  - Klotho (KL) β-glucuronidase, alleles influence coronary artery disease frequency
  - Superoxide dismutase (SOD) and catalase (CAT) increased activity increases life-span via ROS capture
  - Hemochromatosis gene (HFE) alleles influence ROS damage via the Fenton reaction

Figure II.5-12: Genes influencing longevity II

ROS production and damage is mostly linked with mitochondrial function. Therefore mitochondrial genes can also affect individual life-span (Figure II.5-13). It has been shown in centenarians that NADH dehydrogenase subunit 2 gene (ND2) accumulates a SNP at position 5178, and similarly 150T polymorphisms and the U, J, UK and WIX haplotypes also accumulate in the aged.
Genes influencing longevity III

- **Mitochondrial genes**
  - Centenarians (9/11) possess SNP at position 5178 of NADH dehydrogenase subunit 2 gene (ND2)
  - Haplogroup cluster frequency differences, U, J, UK, WIX were frequent in aged; whereas H, HV were rare
  - 150T polymorphism accumulates in aged, though significantly influenced by SNPs 489C and 10398G

Figure II.5-13: Genes influencing longevity III

Genes affecting age related diseases have also been linked with longevity (Figure II.5-14). Concerning apolipoprotein E, the ApoE-ε4 allele is infrequent, while the ApoC3 promoter CC polymorphism accumulates in the aged. Similar to the above certain cholesterol ester transferase alleles that beneficially affect LDL and HDL particle size and the microsomal transfer protein (MTP) 493 G6T variant both show allele preference among long-lived healthy individuals. Prolyl isomerase (PIN1), a protein folding chaperone related with the development of Alzheimer’s disease also exhibits specific genetic accumulation among healthy aged individuals.

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Figure II.5-14: Aging genes conserved in animal kingdom
6. Cancer and tumor development, senescence and cancer, epidemiology and statistics

Certain mammalian species of relatively large body mass, including humans, are long-lived. For this purpose, mammalians harbor stem cells in order to clonally replenish tissues. As a result extended mean life-span is attributed with the increased incidence of cancer development, partly due to the prolonged exposure of clonally expanding stem cells to mutagenic factors, compared to short-lived animals almost exclusively composed of postmitotic cells (i.e. insects). Tumor development is efficiently halted by tumor suppressor genes. This chapter will discuss the ambivalent role of certain tumor suppressor genes in cancer and longevity program / senescence response (Figure II.6-1, Figure II.6-2 and Figure II.6-3).

Figure II.6-1: DNA damage-triggered cell fate responses
6.1. Tumor suppressor genes

Tumor suppressor genes are divided into two major groups (Figure II.6-4). Members of the first group are called caretakers. These belong to the first line of defense as they prevent genomic oncogenic mutations to occur. Should this be circumvented the second group or second line of defense of tumor suppressor genes called gatekeepers eliminate cells with oncogenic mutations by either senescence or apoptosis. This suggests a double
role for gatekeeper-type tumor suppressor genes in cancer development and longevity that is fortunately difficult to circumvent by cancer cells (Figure II.6-5, Figure II.6-6 and Figure II.6-7).

**Tumor suppressor genes**

- **Caretakers**
  First line of defense, prevent genomic oncogenic mutations to occur

- **Gatekeepers**
  Second line of defense, eliminate (by apoptosis) or senesce cells with oncogenic mutations

Figure II.6-4: Tumor suppressor genes

Figure II.6-5: Cancer stem cells escape routine elimination
6.2. The ambivalent role of p53

p53 is perhaps the best characterized tumor suppressor gene. It is a potent inducer of apoptosis, cell cycle arrest and senescence (Figure II.6-8). Statistics highlight the significance of p53 in tumor development: 50% of sporadic malignancies share loss or mutation of p53 gene and 80% of all human cancers have dysfunctional p53 signaling. Moreover, humans heterozygous for p53 deficiency (Li-Fraumeni syndrome) have increased cancer incidence (50% by the age of 30 years) and homozygous loss of p53 is lethal.
**p53 has ambivalent talents I**

- p53 as major tumor suppressor gene
  - Potent inducer of apoptosis, cell cycle arrest, senescence
  - 50% of sporadic malignancies share loss or mutation of p53 gene
  - 80% of all human cancers have dysfunctional p53 signaling
  - Heterozygous human p53 KO (Li-Fraumeni syndrome) have high cancer incidence (50% by 30y)

Figure II.6-8: p53 has ambivalent talents I

However, p53 has other functions related with senescence (Figure II.6-9). Increased p53 activity can lead to accelerated or even premature aging. Partly because p53 activity has profound effects on stem cell proliferation and regenerative capacity in the elderly. It has been proved that p53 signal transduction has crossover with IGF-1 and mTOR signal transduction pathways. Moreover, depending on p53 activity in humans, beyond the age of 60-80 years cancer incidence drops and pro-aging characteristic begin to dominate.

**p53 has ambivalent talents II**

- p53 as pro-aging factor
  - Increased p53 activity leads to signs of accelerated, even premature aging
  - Beyond age 60-80y cancer incidence drops and pro-aging characteristics dominate
  - Signal transduction crossover with IGF-1 and mTOR signaling, explains effects on longevity
  - p53 dosage has profound effects on stem cell proliferation and regenerative capacity in the aged
It is of note that p53 polymorphisms affect both cancer development and longevity (Figure II.6-10). Replacement of proline to arginine at codon 72 results in higher apoptotic efficiency, but simultaneously decreases survival odds. (Over 85 years of age Pro/Pro increases survival chances by 40% despite 2.5x odds for cancer development). The presence of G allele in Mdm2 gene means more suppression and increased cancer development rate compared to the T allele. The combination of G/G and Pro/Pro with smoking means over 10x odds for cancer development, demonstrating the synergistic effects of predisposing genetic set and environmental exposure.

**p53 polymorphisms in cancer and longevity**

- **Codon 72**, proline → arginine, (evolutionarily late SNP), higher apoptotic efficiency
- **Mdm2 gene**, G allele means more suppression and more cancer compared to T allele
- **Combination of G/G, Pro/Pro, smoker means** >10× odds for cancer (gene + environment)
- >85y Pro/Pro means **40% ↑ in survival** despite 2.5× odds for cancer

**6.3. Antagonistic pleiotropy and tumor suppressor genes**

Classical antagonistic pleiotropy trade-off pattern is observed with major tumor suppressor genes like p53 or p16 (Figure II.6-11). The senescence response suppresses tumors and senescence inducers are oncogenic. Cancers are known to frequently share mutations in p53 or p16 genes. The loss of senescence response often leads to cancer development. These correlations outline classical trade-off between cancer development and senescence and specific genetic settings favor one or the other providing selective evolutionary advantage at different ages, as they represent opposing survival strategies.
Antagonistic pleitropy: p53 and p16

- Senescence responses suppress tumors
- Senescence-inducers are also oncogenic
- Cancers share mutations in p53 or p16
- Loss of senescence response = tumor
- Classical trade-off relation

Figure II.6-11: Antagonistic pleitropy: p53 and p16

6.4. Epidemiology and statistics

Currently it is estimated that 13 million cancers are diagnosed every year (excluding non-invasive cancers) and 8 million people die of cancer worldwide (Figure II.6-12, Figure II.6-13). Cancer types account for almost 15% of all deaths; the five most common cancer types listed in decreasing incidence order are the following: lung cancer (1.5 million deaths), stomach cancer (0.8 million deaths), colorectal cancer (0.6 million deaths), liver cancer (0.6 million deaths), and breast cancer (0.5 million deaths). This high incidence rate of cancer development makes invasive cancer one of the primary causes of death in the developed world and secondary leading cause of death in the developing world. At present already half of cases occur in the developing world. Global cancer rates are increasing primarily due to aging societies, but also due to lifestyle changes. Nevertheless the most significant risk factor associated with cancer development is old age. Although it is conceivable for cancer to cause a disease at any age, yet the vast majority of patients diagnosed with invasive cancer are over the age of 65. In fact as recently pointed out by cancer researcher Robert A. Weinberg, “If we lived long enough, sooner or later we all would get cancer.” Association between senescence and cancer is attributed to immunological senescence, increasing number of unrepaird errors accumulating in DNA over time, and age-related endocrine changes. Currently and in the future slow-growing cancers are becoming particularly common. Autopsy studies show that 1/3 people have undiagnosed thyroid cancer at the time of their deaths, and that 4/5 of men develop prostate cancer by age 80. These mostly harmless cancers found during autopsy are often very small and are not related to the person's death. Identifying them would equal with over-diagnosis placing significant burden on an already under-financed and abused medical care systems.
Cancer statistics

- 13 million cancers every year, 8 million deaths
- Most frequent cancer types:
  - Lung cancer
  - Stomach cancer
  - Colorectal cancer
  - Liver cancer
  - Breast cancer
- Most patients are aged 65+ years
  - 1/3 person has thyroid cancer at autopsy
  - 4/5 men have prostate cancer by 80 years of age

7. Alterations of genome due to aging
Like all organic macromolecules, genomic DNA is constantly attacked and mutated by ROS produced as by-products of respiratory chain reaction in the mitochondria. Constant changes require constant repair activity in order to maintain genomic stability that is an important and tough job in long-lived species like humans.

7.1. Oxidative DNA damage and its repair

It is estimated that over 10,000 DNA lesions occur in every cell, every day (Figure II.7-1, Figure II.7-2 and Figure II.7-3). There is significant variety of DNA damage types, over 50 types have been grouped in to five major categories including oxidized purines, oxidized pyrimidines, abasic sites, single- and double strand breaks (Figure II.7-4, Figure II.7-5). Similarly repair types are also numerous and may be grouped into categories. The most often used subtype of DNA damage repair is BER (Base Excision Repair) (Figure II.7-6). BER has two major subtypes; one is AP endonuclease- while the other is lyase-dependent. Another repair subtype removes oxidized purines, mainly 8-oxodG and formamido-pyrimidines. Specialized machinery removes oxidized pyrimidines that would otherwise exhibit strong block of gene expression and are also strongly cytotoxic. Another group is devoted to repair abasic sites, which is the most frequent damage type, in an AP endonuclease-dependent fashion. A further repair type is specialized on single strand breaks that occur 10x more frequently than double strand breaks (Figure II.7-7). Of note is the fact that mtDNA is extremely prone to suffer mutations partly due to limited mtDNA repair. In fact only the nuclear encoded OGG1 and POLG enter the mitochondria to participate in such a quest. NER (Nucleotide Excision Repair) is transcription coupled as active genetic sequences are repaired en route, making this oxidative DNA damage repair type one of the most exotic.

Figure II.7-1: DNA damage: causes, results I
Oxidative DNA damage

- > 10,000 DNA lesions / cell / day
- A variety of DNA damage types (> 50 types)
  - 5 distinctive groups
    - Oxidized purines
    - Oxidized pyrimidines
    - Abasic sites
    - Single-strand breaks
    - Double-strand breaks

Figure II.7-2: Oxidative DNA damage

Figure II.7-3: DNA damage: causes, results II
Non-oxidative DNA damage

• Depurination and depyrimidination
• Deamination
• Single-strand breaks
• Spontaneous methylation
• Glycation
• Cross-linking

Figure II.7-4: Non-oxidative DNA damage

Non-oxidative protein damage

• Biosynthetic errors
• Transcriptional errors
• Translational errors
• Racemization and isomerization
• Deamidation (asparagine and glutamine)
• Reactive carbonyl groups (non-oxidative)
• Serine dephosphorylation

Figure II.7-5: Non-oxidative protein damage
Oxidative DNA damage repair types I

- Base excision repair (BER) is most important, subtypes: AP endonuclease or lyase repair
- Removal of oxidized purines (two types of lesions: 8-oxodG and formamido-pyrimidines)
- Removal of oxidized pyrimidines (strong block, strongly cytotoxic)
- Repair of abasic sites (most frequent) by AP endonucleases

Figure II.7-6: Oxidative DNA damage repair types I

Oxidative DNA damage repair types II

- Repair of strand breaks (single-strand breaks occur 10x more frequently than doubles)
- Limited mitochondrial DNA repair (nuclear encoded proteins of OGG1, POLG)
- Nucleotide excision repair (NER) that is transcription-coupled repair of active genes

Figure II.7-7: Oxidative DNA damage repair types II

Numerous genes are known to be related with oxidative DNA damage repair. These may be grouped based on their lethality in KO animals (Figure II.7-8). Lethal deficiencies include those of APE1, FEN1, POLB, LIG1, LIG3 and XRCC1. Viable KO mutants may be generated for OGG1, NTHL1, MYH and ADPRT. Severity of loss of function has not been tested for NEIL1, 2, 3, TDG, SMUG1 and APE2.
**Genes related to oxidative DNA damage repair**

- Defect is lethal: APE1, FEN1, POLB, LIG1, LIG3, XRCC1
- Defect is viable: OGG1, NTHL1, MYH, ADPRT
- Severity not tested: NEIL1, 2, 3, TDG, SMUG1, APE2

Figure II.7-8: Genes related to oxidative DNA damage repair

**7.2. DNA damage and its repair in progeria**

Premature aging syndromes are also called progeria syndromes. In many of these diseases it is impaired DNA repair that leads to genomic instability and the development of progeria (Figure II.7-9, Figure II.7-10). Major progeria diseases include Werner syndrome, Cockayne syndrome and Hutchinson-Guilford progeria syndrome.

**Genomic instability in progeria types**

- Werner-syndrome
- Cockayne syndrome
- Hutchinson-Guilford progeria
- Xeroderma pigmentosum

Figure II.7-9: Genomic instability in progeria types
Oxidative DNA damage repair and aging

- Elevated cancer frequencies
- Werner syndrome (anti-recombinase)
- Cockayne syndrome (TCR)
- XPD and XPA (repair deficiency)
- Base excision repair (BER) defect is lethal
- Back-up repair pathways

Figure II.7-10: Oxidative DNA damage repair and aging

Werner syndrome is homozygous recessive and mainly affects the skin, but can also cause cataract formation, diabetes mellitus and osteoporosis (Figure II.7-11). Pathology is caused by the WRN protein that has anti-recombinase, helicase functions and removes recombination and repair intermediates. In Werner syndrome WRN shows defective transcription by 50%. WRN interacts with p53 causing attenuated apoptosis as well as increased telomere loss rate.
Werner syndrome

- **Homozygous recessive** (*skin, cataract, diabetes mellitus osteoporosis*)
- **WRN protein** (*anti-recombinase, helicase, removes recombination and repair intermediates*)
- **Defective transcription** (50%)
- **Relation with p53** (*attenuated apoptosis*)
- **Increased telomere loss rate**

Figure II.7-11: Werner syndrome

Cockayne syndrome is a rare segmental progeria that causes dwarfism, photosensitivity and neuronal degeneration (Figure II.7-12: Cockayne syndrome). The cause of the disease is deficiency in transcription coupled repair (TCR). This leads to defective 8-oxodG excision by 50%. Interestingly global genome repair (GGR) remains proficient.
Cockayne syndrome

- Rare segmental progeria (dwarfism, photosensitivity, neurological degeneration etc.)
- Defect in transcription coupled repair (TCR)
- Defective 8-oxodG excision (50%)
- Subtypes: CS-A, CS-B
- Global genome repair (GGR) is proficient

Hutchinson-Guilford progeria syndrome (HGPS) is caused by laminA mutation that leads to increased nuclear envelope fragility (Figure II.7-13: Hutchinson-Guilford progeria syndrome). This progeria syndrome affects mesenchymal cells and leads to premature death.

Hutchinson-Guilford progeria syndrome

- Lamin A mutation (nuclear envelope fragility)
- Primarily affects mesenchymal tissues
- HGPS cells have decreased stress resistance
- Rapid progeria, premature death
8. Molecular / cellular effects of acute and chronic stress

Acute severe stress is known to induce either necrosis or apoptosis. However, the effect of moderate chronic stress is different, under certain conditions this leads to the accumulation of beneficial effects. An example is the case of calorie restriction (CR).

8.1. CR extends life-span

It has been known since decades that calorie restriction can significantly extend the life-span of laboratory rodent models like the mouse (Figure II.8-1, Figure II.8-2). To a certain extent CR increases life-span proportional with the degree of calorie restriction. Beneficial effects are detectable up to 65% cut in energy intake (the maintenance of micronutrient balance is of key importance during such experiments). Most studies report an optimal gain at 30-50% cut in energy intake compared to ad libitum fed animals (Figure II.8-3). CR extends both mean life-span and maximal life-span (this latter is of key importance and emphasizes the significance of CR mechanisms). CR can increase health-span as well via opposing the effects of diseases like cardiovascular disease, cancer, neuronal disease diabetes, renal disease etc. The underlying molecular mechanisms have also been clarified (Figure II.8-4, Figure II.8-5 and Figure II.8-6). Apparently the major mechanism through which CR extends life-span is achieved via decrease in ROS production (reduced mitochondrial proton leak). Less energy consumed requires less respiratory burden on mitochondria that can function at increased efficiency. ROS production is detrimental on the long term stability of macromolecules including nucleic acids, proteins, lipids, sugars etc. Such alterations severely affect post-mitotic cells of long life-span in which oxidized macromolecules accumulate lacking dilution during subsequent cycles of cell division.

Figure II.8-1: CR increases life-span
Figure II.8-2: Lifespan increase due to CR

**CR extends life-span**

- Reducing food-consumption by 30-50% increases mean and maximum life-span
- Opposes cancers, diabetes, renal disease, cardiovascular disease, neuronal diseases
- Major mechanism of action: decrease in ROS production (reduced mitochondrial proton leak)

Figure II.8-3: CR extends life-span
CR extends life-span via:

- Insulin / IGF1 signaling pathway
- Sirtuin signaling pathway
- Redox signaling pathway
- TOR signaling pathway

Figure II.8-4: CR extends life-span via…

Insulin / IGF signaling pathway

- Subset of daf genes dramatically increase life-span
- Main target is daf16 that is highly homologous with Foxo
- Insulin and growth-factor reduction shifts Foxo proteins to nucleus
- CR induces 50% decrease in insulin plasma levels
- CR induces 20% decrease in plasma IGF1 levels

Figure II.8-5: Insulin / IGF signaling pathway
Proof of GH / IGF signaling axis in aging

- Snell and Ames mice (lack of GH, PRL, TSH) have increased life-span
- GHRH, GHR, IGF1R deficient mice have increased life-span
- p66shc (IGF1R substrate) deficient mice have increased life-span
- Klotho (IGF1-repressor)-transgenic mice have increased life-span

Figure II.8-6: Proof of GH / IGF signaling axis in aging

8.2. Reproducibility of CR effects

The beneficial effects of CR on life-span values have been tested on other species and also on wild-type animals. Reproducibility is not as straightforward as one would expect. In the case of the laboratory mouse, preferred strains include quickly reproducing species that achieve relatively higher body size and weight. However, wild type mouse strains are different as their reproductive rate is lower just like adult body size and weight. Hence beneficial effects of CR are difficult to reproduce in wild type or back-crossed strains compared to inbred laboratory mouse species. So it is possible that beneficial effects that appear obvious at first glance mostly counteract the negative collateral effects of selection pressure on inbred laboratory mouse strains with increase in reproductive rate, body size and weight.

8.3. CR and antagonistic pleiotropy

Antagonistic pleiotropy is a theory of aging that reappears in numerous fields of aging research. Calorie restriction is also a field that fits the theory of antagonistic pleiotropy according because a species can choose between two radically different strategies. One invests energy into quick development, maturation and reproductive rate like in the case of laboratory mouse strains. The other strategy invests less energy into accelerated development, maturation and reproductive rate; instead care is taken to efficiently maintain long term genomic stability as well as the healthy status of postmitotic cells. The latter strategy is more characteristic of wild type strains. In fact the two strategies are not strictly delineated genetic programs and transition exists from one to the other. This is represented by CR in the case of laboratory mouse strains that allows for a shift towards increased longevity.

9. Metabolism and longevity I

It has been confirmed by numerous studies on several occasions that metabolism and longevity are deeply interconnected. It has been discussed in the chapter dealing with mitochondrial senescence that increasing energy turnover also increases the production / leak of ROS that severely damage neighboring macromolecules of mitochondria and other cellular organelles. Therefore one can predict a correlation between energy turnover and senescence rate. This is in fact the case at the level of both single cells and entire multicellular organisms.

9.1. Antagonistic pleiotropy
In fact the inverse correlation between energy turnover and longevity may be explained at an evolutionary level by the theory of antagonistic pleiotropy. According to this theory a multicellular organism may choose between two strategies. It may live along with a high energy turnover accompanied by accelerated pace of aging, countered by rapid breeding turnover. The other strategy involves emphasis on long lasting efforts keeping genomic stability and continuous maintenance functions accompanied by lower energy turnover and slower breeding turnover. In fact the switch between these two programs is fulfilled by SIRT2 genes discussed elsewhere.

**9.2. Protein peroxidation, repair, associated diseases**

Proteins are macromolecules that are affected by ROS (Figure II.9-1). Oxidative stress may cause damage of multiple types including MDA-lysine adducts (also serving as markers), oxidation of the protein backbone and formation of protein cross-links. This latter process will be discussed in detail in the chapter on senescence-related intercellular / intracellular pathologies as cross-links are characteristic to aged proteins with problematic or impaired breakdown processes. Protein peroxidation may also affect amino acid side chains and protein fragmentation.

### Protein peroxidation

- MDA-lysine adducts as markers for protein oxidative stress level
- Oxidation of protein backbone
- Formation of protein cross-linkages
- Oxidation of amino acid side chains
- Protein fragmentation

Figure II.9-1: Protein peroxidation

Repair of protein peroxidation process is limited (Figure II.9-2). Direct repair means the re-reduction of oxidized sulfhydryl groups. Indirect processes include the recognition, removal and degradation of protein peroxidation products via the proteasome, calpain or the lysosome. This is then followed by replacement and re-utilization. If – for any reason – repair processes fail protein peroxidation products readily form lipofuscin that also called age pigment or ceroid in cells.
Repair following protein peroxidation

- Direct: re-reduction of oxidized sulfhydryl groups
- Indirect:
  - Recognition, removal, degradation (proteasome, calpain, lysosome)
  - Replacement, re-utilization
- Storage as lipofuscin (age pigment, ceroid)

Proteins are basic components of all life-related molecular chains of events. Therefore, as anticipated, the increased formation of protein peroxidation products may be associated with various diseases. Of note many of these are central nervous system diseases (Figure II.9-3). Possible reasons include that nervous tissue is highly energy dependent becoming a strong source and target of ROS. Also, neurons are typical postmitotic cells that live long enough to accumulate protein peroxidation products, leading to lipofuscin accumulation and functional impairment. Other affected tissues include the endothelium and the cardiovascular system, locations of permanent mechanical stress. The mentioned diseases include Alzheimer’s, Parkinson’s, atherosclerosis, progeria subtypes, diabetes and cataract formation.

Protein peroxidation and diseases

- **Increased levels of oxidized proteins**
  Alzheimer’s disease, ALS, cataract, RA, muscular dystrophy, RDS, progeria, Parkinson’s disease, Werner syndrome

- **Elevated content of modified proteins**
  Cardiovascular, Alzheimer’s disease, atherosclerosis, Parkinson’s disease

- **Increased levels of protein glycation / glycoxidation**
  DM, atherosclerosis, Alzheimer’s disease, Parkinson’s disease

- **Elevated content of protein nitrotyrosine damage**
  Alzheimer’s disease, SM, lung injury, atherosclerosis
9.3. PUFA controversy

It is recently rather fashionable to consume dietary additives that contain PUFA (poly-unsaturated fatty acids) like AA (arachidonic acid) or DHA (docosahexaenoic acid). However, it is of note that only minor quantities of additives represent beneficial effects, increase quantities have been shown to cause detrimental effects in vivo including increased ROS production in mitochondria, atrial fibrillation, neurological damage, increase protein peroxidation, apoplexy etc (Figure II.9-4, Figure II.9-5). All these events are due to PUFA’s capability of participating in long free radical chain reactions, extending the active radius of ROS. Indeed, DBI (Double Bond Index) supports this process. Long lived animal species share lower DBI compared to short lived animals with elevated DBI. It appears that membranes may act as pacemakers of overall metabolic activity. The theory of homeoviscous longevity adaptation explains the process of increasing MLSP (mean life-span) by gradually replacing PUFA with more saturated fatty acids in membranes thus limiting the active radius of ROS.

**Lipid peroxidation**

- PUFA residues are sensitive to ROS
- PUFA are both ROS targets and mediators
- PUFA content of mt membrane affects life-span

Figure II.9-4: Lipid peroxidation

**PUFA controversy: AA and DHA**

- **HOMEOVISCOUS LONGEVITY ADAPTATION**
- DBI negatively correlates with size and MLS
- Detrimental in vivo (mt, heart, neural system etc.)
- SAM-P strain with increased AA and DHA levels
- MDA-lysine adducts as markers for protein oxidative stress level

Figure II.9-5: PUFA controversy: AA and DHA

10. Metabolism and longevity II.

Metabolism and longevity have long been proved to be related. We have already discussed in previous chapters how calorie restriction and peroxidation processes affect longevity via metabolic routes. This chapter discusses the molecular biological background of how CR and decreased metabolic rate prolong life-span.
10.1. Sirtuins as master regulators

Sirtuins are a family of genes that have been best characterized in yeast (Figure II.10-1, Figure II.10-2). The archetype of sirtuins is the Sir2 gene of yeast. Sirtuins are evolutionarily highly conserved genes involved in the regulation of transcriptional silencing especially in silencing telomeres and rDNA repeats (sirtuins are components of the RENT silencer complex at telomeres) (Figure II.10-3, Figure II.10-4). Sirtuins also affect silencing via the formation of heterochromatin, a more condensed and hence less accessible form of genomic DNA. Sirtuins share an H4-specific deacetylase (NAD-dependent) activity, further influencing genomic DNA activity indirectly. The fact that sirtuins depend on NAD availability in yeast and NAD / NADH ratio in mammals confirms sirtuins being energy sensors that link metabolism and aging.

Figure II.10-1: The mechanism of action for sirtuins
Features of Sir2 family

- Sir2 family proteins, called ‘sirtuins’
- Regulation of transcriptional silencing
- Silences telomeres, rDNA repeats
- Component of RENT silencer at telomeres
- Forms heterochromatin
- ADP-ribosyl transferase activity
- H4-specific deacetylase (NAD-dependent)
- Energy sensor, links metabolism and aging

Figure II.10-2: Features of Sir2 family

Figure II.10-3: Acetylation status and epigenetic silencing
10.2. Mammalian sirtuins

Mammalian sirtuins have seven members, Sirt1-7 (Figure II.10-5). Mammalian Sirt1 is the homologue of yeast Sir2 gene. Sirt1 mediates most life-extending effects of calorie restriction. It mediates beneficial effects in multiple organs via several routes. In the pancreas it improves glucose tolerance and insulin sensitivity, represses Ucp2 and deacetylates Foxo1 (Figure II.10-6). In the liver sirtuin1 promotes gluconeogenesis and inhibits glycolysis and deacetylates PGC-1α. In white adipose tissue (WAT) it interacts and represses PPARγ and increases adiponectin secretion. In skeletal muscles sirtuin1 regulates glucose uptake and insulin sensitivity (Figure II.10-7). In the central nervous system it can ameliorate the symptoms of Alzheimer’s, Parkinson’s and Huntington disease.

Sirtuins as regulators for aging

- Highly conserved enzymatic core domain
- Mediates life-extending effects of CR
- Mammals have 7 sirtuins, Sirt 1-7
- Sirt1 shows highest homology with yeast Sir2
**Sirt1 as regulator for aging I**

- Pancreas: improves glucose tolerance and insulin sensitivity, represses Ucp2, deacetylates Foxo1
- Liver: promotes gluconeogenesis and inhibits glycolysis, deacetylates PGC-1a
- Fat (WAT): interacts and represses PPARγ, increases adiponectin secretion

Figure II.10-6: Sirt1 as regulator for aging I

**Sirt1 as regulator for aging II**

- Muscle: regulates glucose uptake and insulin sensitivity, effect also achieved via resveratrol
- Brain: beneficial in degenerative diseases like Alzheimer’s, Parkinson’s, Huntington

Figure II.10-7: Sirt1 as regulator for aging II

Sirtuins also affect stress resistance and response (Figure II.10-8). Sirt1 deacetylates p53 thus inhibits apoptosis and promotes cell survival. It also deacetylates Foxo family members affecting DNA-damage repair, cell-cycle arrest and again, apoptosis. The deacetylation of NF-κB, a pro-survival transcription factor increases cellular life-span as well (although the effects of NF-κB are context dependent).
**Sirt1 and stress resistance**

- Deacetylates p53, inhibits apoptosis, promotes cell survival
- Deacetylates Foxo family members affecting DNA-damage repair, cell cycle arrest, apoptosis
- Deacetylates NF-kB, a prosurvival transcription factor (context dependent)

Figure II.10-8: Sirt1 and stress resistance

10.3. Functional listing of further mammalian sirtuins

Other mammalian sirtuins have also diverse, significant effects (Figure II.10-9, Figure II.10-10, Figure II.10-11). Sirt2 product is cytoplasmic, functions as a sort of tumor suppressor. Sirt3-5 are mitochondrial proteins involved in thermogenesis by brown adipose tissue (BAT), response to amino acids, and developmental processes in thymocytes, respectively. Sirt6-7 encodes nuclear proteins involved in DNA repair and genome stability.

**Properties of other mammalian sirtuins**

- Sirt2: cytoplasmic, tumor suppressor gene
- Sirt3: mitochondrial, thermogenesis in BAT
- Sirt4: mitochondrial, response to amino acids
- Sirt5: mitochondrial, high in thymus, lymphoblasts
- Sirt6: nuclear, DNA repair, genome stability
- Sirt7: nucleolar, lacks enzymatic activity

Figure II.10-9: Properties of other mammalian sirtuins
Redox signaling pathway

- Changes in redox signaling may be more important than oxidative damage?
- Redox sensitive transcription factors include NF-κB, Nrf2, HIF1
- Thioredoxin and glutathione systems modulate redox status
- Aging decreases GSH and thioredoxin levels
- CR increases GSH and thioredoxin levels

TOR signaling pathway

- TOR (target of rapamycin), evolutionarily highly conserved, regulates cell growth
- Targeted deletions increase life-span
- Daf-16 dependent, requires Foxo
- Reduction (Ames dwarf mouse) leads to decreased ROS production

10.4. Sirt1 mimetic compounds

Currently few pharmacological sirtuin-mimetic drugs are known (Figure II.10-12, Figure II.10-13, Figure II.10-14, Figure II.10-15 and Figure II.10-16). These include resveratrol, qercetin and piceatannol. Of these compounds by far resveratrol is the most characterized and acknowledged. The natural source of resveratrol is red grape and red wines produced from red grapes. Resveratrol can efficiently mimic the beneficial effects of CR, even among high-fat diet consumers (phenomenon known as French paradox). Resveratrol has cardioprotective, neuro-protective and also cancer suppressing activities that make its advantageous characteristics so much similar to CR (Figure II.10-17, Figure II.10-18).
Resveratrol

- Currently few pharmacological Sirt1 mimetics are known: resveratrol, qercetin, piceatannol
- Natural source: red grapes / wine; cardio-protective, neuro-protective, cancer suppressing
- Can efficiently mimick certain CR-induced positive effects despite high-fat diet

Figure II.10-12: Resveratrol increases life-span

Figure II.10-13: Resveratrol
Figure II.10-14: Resveratrol / paclitaxel combination in cancer

Figure II.10-15: Mechanism of action for GH / IGF pathway
Figure II.10-16: Environmental effects in expected life-span

Figure II.10-17: Sirtuin switch in ad libitum and CR mice
Sirt1 and CR

- Several beneficial effects of CR effectuated through sirtuins
- CR induces eNOS and NO, upregulating Sirt1 and mitochondrial biogenesis
- Affects brain activity and indirectly physical activity

Figure II.10-18: Sirt1 and CR

11. Senescence-related intercellular / intracellular pathologies

During senescence protein turnover rate is significantly altered. This often leads to the accumulation of oxidized protein breakdown by-products in both intracellular and extracellular spaces. If this process exceeds a threshold level then pathologies may develop. Neurons are long-lived postmitotic cells in which division cannot dilute protein breakdown by-products that accumulate with time. The resulting potential pathologies include Alzheimer’s and Parkinson’s disease, but also Huntington disease and prion protein-related diseases (i.e. CJS) (Figure II.11-1, Figure II.11-2, Figure II.11-3, Figure II.11-4, Figure II.11-5, Figure II.11-6).

Figure II.11-1: Post-translational life of proteins
Non-oxidative DNA damage

- Spontaneous changes
- Depurination and depyrimidination
- Deamination
- Single-strand breaks
- Spontaneous methylation
- Glycation
- Cross-linking
Non-oxidative protein damage

- Biosynthetic errors
- Transcriptional errors
- Translational errors
- Racemization and isomerization
- Deamidation (asparagine and glutamine)
- Reactive carbonyl groups (non-oxidative)
- Serine dephosphorylation

Figure II.11-4: Non-oxidative protein damage

Modulation of non-oxidative protein damage

- Protein turnover (high turnover = anti-aging strategy due to dilution)
- Increased levels of stress proteins, chaperons, ubiquitin (hormesis, training)
- Intramitochondrial proteolysis (Lon protease for miscoded and oxidized proteins, EGF↑)

Figure II.11-5: Modulation of non-oxidative protein damage
**Transcriptional and translational dysregulation in aging**

- Transcriptional alterations, activity \( \downarrow \) by 15-30%
- tRNA and aminoacylation
- mRNA processing and stability, \( \downarrow \) total poly(A+)
- Translational alterations, \( \downarrow \) protein synthesis, but calorie restriction can reinforce protein synthesis
- Efficiency and accuracy of protein synthesis \( \downarrow \)
- Initiation, elongation, termination during protein synthesis, EF1a-activity \( \downarrow \) by 35-45%

Figure II.11-6: Transcriptional and translational dysregulation in aging

### 11.1. Lipofuscin or lysosomal waste

Lipofuscin is also called age pigment or ceroid (Figure II.11-7). When overwhelmed or hypoactive (due to i.e. senescence) lysosomes fail to digest aged macromolecules. Intracellular waste material forms brown-yellowish, autofluorescent, electron-dense granules called lipofuscin. Macromolecules that form lipofuscin are mostly oxidized proteins, a process potentially accelerated by the presence of iron. Not surprisingly, mitochondria are the major generators of lipofuscin as both ROS leak and iron containing proteins are provided by mitochondria. Lipofuscin can occupy significant proportion of intracellular space before impairing cellular functions: it has been reported that as much as 75% of perikaryon may be filled with lipofuscin in senescent, functional neurons. Beyond the threshold level, lipofuscin and other mostly protein-related breakdown by-products can lead to the formation of amyloid fibrils that can amplify in quantity leading to the above, mostly neuronal degenerative diseases.
Lipofuscin, lysosomal waste

- Lysosomes fail to digest all aged macromolecules
- Waste: brown-yellow, autofluorescent, electron-dense, granules called lipofuscin, ceroid, age-pigment
- Increased oxidation, especially in presence of iron
- Mitochondria are major generators of lipofuscin
- May occupy up to 75% of perikaryon in neurons
- Forms amyloid, role in Alzheimer’s, Parkinson’s

Figure II.11-7: Lipofuscin, lysosomal waste

11.2. Amyloid aggregates

Amyloid fibrils are extracellular protein aggregates formed by Aβ plaques (Figure II.11-8, Figure II.11-9, Figure II.11-10, Figure II.11-11). Amyloid aggregates may originate from several protein types that eventually lead to the formation of rather uniform aggregates. Historically amyloid aggregates were assumed to be composed of carbohydrates due to the staining pattern similar to starch. The formation of amyloid aggregates has two phases: lag phase and growth phase. During lag phase native, denatured monomers and oligomers are converted into each other maintaining equilibrium. However, exceeding a threshold level of oligomers triggers the growth phase of amyloid filaments, protofibrils and fibrils. If these accumulate in significant quantities these may trigger the development of degenerative neuronal disease including Alzheimer’s, Parkinson’s and Huntington.
Figure II.11-8: Neuronal EC Aβ plaques and their effects

Figure II.11-9: Amyloid fibril development and growth
Figure II.11-10: Amyloid fibrils by AFM
11.3. Proteasome function and senescence

The proteasome is one of the major intracellular protein breakdown complexes, the main non-lysosomal proteolytic machinery (Figure II.11-12). It has several activities including chymotrypsin-like (CT-like), trypsin-like (T-like) and peptidyl-glutamyl peptide hydrolase (PGPH) activities. The proteasome serves not only housekeeping functions but is also actively involved in apoptosis, cell cycle and cell differentiation control.
Proteasome function

- Main non-lysosomal proteolytic machinery
- Activities include:
  - Chymotrypsin-like (CT-like)
  - Trypsin-like (T-like)
  - Peptidyl-glutamyl peptide hydrolase (PGPH)
- Not only housekeeping, but also involved in:
  - Apoptosis
  - Cell cycle
  - Cell differentiation

During senescence the proteasome degradation balance is overwhelmed, partly by the augmented load of increasingly modified macromolecules and also because the proteasome functions at lowered efficiency (Figure II.11-13). Calorie restriction, the most acknowledged lifespan-extending intervention has been recorded to increase proteasome functionality (Figure II.11-14, Figure II.11-15). CR can restore PGPH activity that is decreased by half at elevated ages and also increases proteasome subunit (Rpt5) and activator (PA28) expression. It is of note that in healthy centenarians proteasome activity is maintained compared to age controlled individuals with diseases.

Proteasome function in aging

- Degradation of oxidized, ubiquitinated proteins
- Proteasome function is compromised in aging
- Increased modification of macromolecules
- Increased load, lowered efficiency leading to immune- and neuronal senescence
CR and non-oxidative protein damage

- CR → fasting → hypoglycemia → decreased EC and IC glycation
- Lower insulin levels, higher proteasome functionality
- Higher NADPH ratio, better maintenance of glutathione in reduced form

Figure II.11-14: CR and non-oxidative protein damage

Proteasome function in CR

- Lower insulin levels, higher proteasome functionality
- CR restores PGPH activity (↓ by 50% in aging)
- Maintains/stimulates proteasome subunit (Rpt5) and activator (PA 28 a subunit) expression
- Healthy centenarians have normal proteasome activity

Figure II.11-15: Proteasome function in CR

The proteasome has also been shown to be involved in immune senescence (Figure II.11-16). Along with aging and immune decline there is decreased IκB degradation and NF-κB activation, and CT-like activity has also been shown to decrease in T-cells. Moreover, the 26S subunit that is central in antigen processing is also modified during senescence.
Proteasome function in immune senescence

- Decreased IkB degradation, decreased NF-kB activation, immune decline
- CT-like activity decreases in T-cells
- Specific modification of 26S subunit, central in antigen processing

Figure II.11-16: Proteasome function in immune senescence

The proteasome function is also a key player in neuronal senescence (Figure II.11-17). CT-like activity drops in most central nervous tissues (with the exception of the cerebellum and the brain stem). Neuronal cells are typical long-lived postmitotic cells that are hence vulnerable for the accumulation and aggregation of damaged proteins that can result in the development of degenerative diseases like Alzheimer's, Parkinson's and Huntington (Figure II.11-18, Figure II.11-19, Figure II.11-20, Figure II.11-21, Figure II.11-22, Figure II.11-23).

Proteasome function in neuronal senescence

- CT-like activity drops (not in cerebellum / brain stem)
- Proteasome decline enhances neuronal vulnerability
- Accumulation, aggregation of damaged proteins
- Increase in Lewis bodies, huntingtin fragments
- Role in pathogenesis of Alzheimer's, Parkinson's
- Amplification of lipofuscin, threshold phenomenon

Figure II.11-17: Proteasome function in neuronal senescence
Figure II.11-18: Autophagy and IC breakdown

Figure II.11-19: Prion protein conversion
Hutchinson-Guilford progeria syndrome

- LaminA mutation (nuclear envelope fragility)
- Primarily affects mesenchymal tissues
- HGPS cells have decreased stress resistance
- Progeria causing premature death

Figure II.11-21: Hutchinson-Guilford progeria syndrome
12. Molecular mechanisms of interventions

One of the most elaborate collection of concepts for life-extension is housed by SENS working in the framework of the Methuselah Foundation. SENS stands for Strategies for Engineered Negligible Senescence (Figure II.12-1). The head organizing person in SENS is Dr. Aubrey de Grey and the SENS headquarters is situated in Cambridge, UK. Below is a short summary of the program of SENS. Much of this is based on technology that does not exist yet, but would likely be invented in the predicted time-frame based on the current rate of biomedical development, allowing us to peek into a possible future scenario.
SENS

• ‘Strategies for Engineered Negligible Senescence’ (Dr. Aubrey de Grey, Cambridge, UK)
• Increase the expected age at death for healthy 55-year old from 85 to 115 years by 2030
• Mimic negligible senescence observed in Hydra

Figure II.12-1: SENS

12.1. Degree of life-extension, planned interventions

The model system of the SENS plan is hydra. Hydra is basically a sack-structured animal mainly composed of stem-like cells and these animals shown only negligible rate of senescence. According to SENS predictions, in the next 20 years (from 2010 to 2030) the increase in mean life-span is expected to increase with 30 years from the current 85 years to 115 years. This significant increase is based on interventions planned to occur at three levels: metabolism, damage and pathology (Figure II.12-2). The planned steps include the clearance of damaged intracellular and extracellular protein aggregates, a major problem of long-lived postmitotic cells like neurons. Senescent cells should also be removed and periodically replenished by telomerase-incompetent stem cells. (Telomerase deficiency should help to prevent the emergence of immortalized cells that could result in cancer.) Finally mutation-prone mitochondrial DNA elements should be shifted into the genomic DNA to prolong the sequence integrity of mitochondrial genes.

SENS: planned interventions

• Intervention to occur at three levels: metabolism, damage, pathology
  - Clearance of damaged IC and EC protein aggregates
  - Removal of senescent cells
  - Telomerase-incompetent stem-cell therapy
  - Escape mitochondrial mutations via shift to gDNA

Figure II.12-2: SENS: planned interventions

12.2. Limitations of SENS
The SENS plan is thorough, science-based, but as with all plans, future will decide how much of it is feasible. One major question about SENS is whether all issues have been addressed to achieve significant life-extension (Figure II.12-3). The process of aging is not clonal but mosaic, and the outlined intervention strategies like stem-cell replenishment is based on clonal replacement. Also, several intervention methods have not been invented yet, at least not in fully tested and detailed form that is required for application in humans. Besides, the gradual loss of genome instability is not addressed by SENS, although this is an acknowledged problem and many consider that crossing the threshold level of genomic instability as the point of no return in cellular senescence. Certainly, SENS is a thorough compilation of intervention strategies, future will decide how much of this can be translated into real achievement measurable in the form human life-extension.

**Limitations of SENS**

- Longest life documented: Jeanne Calment, 122y
- Have all questions been addressed?
- Aging is not clonal (not cancer), but mosaic
- Gradual loss of genome instability is inevitable

Figure II.12-3: Limitations of SENS

**13. Recommended literature**


Aging of the Genome, the Dual Role of DNA in Life and Death Editor: Jan Vijg Publisher: Oxford University Press, ISBN 978-0-19-856922-0