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Overview

Aging

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Abstract

The paper deals with changes of human organism during physiological aging. Initially changes occur in internal organ function, followed by morphological changes of particular organs. The body start showing signs of growing old at the beginning of the fourth decade. Some organs age faster as the kidneys, while others age slower such is the liver. Among the general changes which occur along with aging, body mass increases as a result of fatt tissue increase, but decreases in highly advancing age. Changes of body water also occur and is reduced by about 10–15 % in comparison to middle-aged persons. The human body contains more extracellular than intracellular water and that is why is greater plasma volume with advancing age. The quantity of the connective tissue in heart muscle increases, particularly in the endocardium and the epicardium, while the pigment lipofuscin is deposited in the myocardium. From the beginning of the fourth decade, cardiac output decreases by about 1% yearly, stroke volume decreases for about 0.7%, and peripheral vascular resistence increases for about 1.2% yearly. In the respiratory system, from the fourth decade the number of cilia diminish, alveolar macrophages are less efficient, lung elasticity decreases, sternocostal joints became inelastic, chest expansion is diminished, the speed of expiratory air can be reduced. In the kidneys changes in blood vessels leading to the alteration of nephron function. The number of capillaries dwindles, influencing both glomerular and peritubular parts, the total weight of the kidneys can be reduced, the connective tissue increases as the basal membrane become thicker. Glomerular capillaries degenerate and are bridging by arterioles. Other internal organs change with advancing age also.

INTRODUCTION

Aging is mostly discussed on the basis of chronological age. That is why the usual definition of the elderly which usually comprises chronological ages of 65 or more, is not valuable any more. Chronological and biological ages are in growing incongruity and it should be strived at determining biological age limit. The aging of the human body start at the beginning of the fourth decade. A chronological age of 65 for the beginning of "elderhood" is a sociopolitical construct developed by social security systems and government organizations to decide an arbitrary age at which benefits should be paid. But, numerous questions are imposed here, such as: can we talk about so-called older age on the basis of the chronological age border of 65 years? Is there substantial proof for this? What criteria are there? Probably, genetic-evolutionary and direct environmental factors over the centuries are responsible for the changes observed in humans *(1–5)*.

It is considered that in the Paleolithic era people lived approximately 18 years; old Egyptians lived about 29 years. Sometimes it is stated that at the time of Christ the average life expectancy was about 30 years, although there were some people of pretty advanced age. In the so-called new era, some 500 years ago, the average life span was about 35 years. At the beginning of the twentieth century, average life expectancy was about 50 years, and at the end of the century it approached almost 80 years. For example, in USA at the beginning of the 20-th century the population aged 65 or older for both genders was 4.1%, in France 8.1%, but two thirds of the way through the century in the USA the proportion had increased to 8.3%, in France 12% and in Croatia 10.8%. It was expected that at the turn of the millennium there would be about 11.4% of the global population belonging to older age groups, but the actual data is much higher. In Croatia 15.62% of inhabitants are currently aged 65 or more, with the assumption that by the year 2050 AD, more than 30% of the population will belong to this group. In the city of Zagreb, every sixth inhabitant is aged 65 or over, and in the period 1992 to 2002 more than 9000 inhabitants died than were born.

CHANGES OF INTERNAL ORGANS

Numerous changes occur in the human organism with advancing age, from decrease in material substrate quantity, making tissues less valuable, and often being replaced by still less valuable tissue *(6–8)*. These changes are called atrophic or degenerative (the so-called "tissue wearing out processes"). Some authors claim that the end of an organism's life is the final course of events in increasing the entropy of a non-regulated system. In recent times the theory of apoptosis - programmed cell death-has been more widely accepted.

What definition leads to the so-called older life age? It is a matter of different approaches, but common to all of them has been the citing of chronological age. An age of 65 years is most often used for assessment of the so-called older age. But, a more careful definition from the WHO (World Health Organization) regards elderly as the range from 65 to 75 years, old age from 76 to 90 years, and very old age as the chronological age over 90 years; often definition of elderly is 60> years; usual definition is 65> years. The highest somatic functional capacity in man is achieved at about the 30th year of life. According to some authors and our data, the aging of the human body does not start at the age of 65, but after the 30th year.

Initially changes happen in internal organ functions, followed by morphological changes of particular organs. Some organs age faster (for example kidneys), some slower (for example liver). When evaluating the changes associated with advancing age, three types of changes can take place: changes of organs due to disease, changes of organs caused by organism aging (the so-called physiological aging), and the simultaneous changes in organs due to both disease and aging process *(9–14)*. This text deals with the organ changes during physiological aging.

TABLE 1

Some parameters indicating biological ages (6).

Parameter	Correlation with biological age
Skin changes	+0.604
Systolic blood pressure	+0.519
Lung vital capacity	–0.402
Strength of fist	–0.323
Time of reaction	+0.488
Sensitivity on vibrations	–0.537
Quick-sightedness	–0.432
Threshold of hearing at 4.000 Hz	–0.596
Serum cholesterol level	+0.234

Incorrect is the Seneca's statement: Senectus ipsa morbus est – elderly is a disease. Some parameters indicating biological age are presented in Table 1.

Among the general changes which happen along with aging, body mass grows with advancing age on account of fat tissue increase, but this normally decreases in highly advanced age. Thus, for example, in some cross-sectional studies, in younger age men fat tissue amounts to about 15% of body mass, and at the age of 75 it is more than 35%; in young women it is more than 30%, while at the age of 75 it is 45% or more, on average. Cross-sectional comparisons of middle and older ages show that the total amount of water in the body is reduced by about 10–15%. The human body contains more water outside than within cells, i.e. there is greater plasma volume. The ratio of these parameters in middle age is about 2:1, but it reduces in older *(1–5,14–16)*.

Cardiovascular system

The heart is susceptible to changes with the increase of biological age. The quantity of the connective tissue i.e. collagen in heart muscle is increasing, particularly in endocardium and epicardium, while the pigment lipofuscin is deposited in myocardium. The strength of cardiac muscle is decreasing, as well as the speed of myocardiac fibres shortening. Inotropic action also decreases, as well as of the diastolic filling pressure, ventricle ejection fraction, while systolic load of the heart increases. By some authors, from the beginning of the fourth decade of life, the cardiac output decreases about 1.0% per year, the stroke volume decreases approximately 0.7% per year, the peripheral vascular resistance increases over approximately 1.2% yearly. This means that, if we compare ages of 30 and 90 years, cardiac output could be decreased for about 60%, stroke volume for about 42%, and peripheral vascular resistance increases for about 72% (*2–7,16–18)*.

The cells of sinoatrial node are replaced by connective tissue; the heart frequency is diminishing, and the heart significantly more slowly reacts by elevating frequency. The capacity of performing physical strains could be doubly reduced with advancing age, both due to the decrease in the cardiac output, in the vital lung capacity, in the amount of auxiliary muscles participating in

breathing, increase in the amount of fat tissue, and the loss of mineral bone content *(6,12,15)*.

In persons aged approximately 90 years, the ability of performing physical strains could be about 70% lower than in the so-called younger age. Having in mind body efforts, about two half an hour daily walks, i.e. about 5 km daily or 24–32 km weekly (if there are no medical limitations) will elevate the heart rate to about 110–120 per minute, what resembles submaximal body strain. The highest heart rate is calculated according to the calculation: 220 – age in years, and is aiming at achieving the so-called submaximal or 85% of maximal heart rate. But, if the so-called elderly person has been practicing physical exercise during life, he/she has a far greater maximal aerobic lung capacity than persons who neither exercise nor walk, but mostly sit. However, persons of the so-called older age, who during life had mostly sedentary jobs, when they start to exercise under the condition that they are clinically examined, assessed by ECG and ergometry and are with no contraindications for physical exercise, they often achieve higher work capacity and increased glucose tolerance. Regarding lipoproteins, sometimes changes could be fourfold: the concentration of "protective" HDL can increase, the concentration of "dangerous" triglycerides, LDL and VLDL can diminish, both can happen as well and rarely, none of these changes would occur. Time will show whether body load brings to the changes of derivates of amino acid methionine--homocysteine, whose elevated concentration also presents risk for atherosclerosis, as are serum elevated level of uric acid, glucose, lipoprotein Lp(a), fibrinogen and C-reactive protein (CRP).

Although by some authors the mentioned changes occur after 30 years of life, it is very often strictly individual, because of the fact that many reductions in organ functions in the so-called older age are less the consequence of aging and more the result of inactivity. In the developed World it is estimated to be 50%. Thus, according to functional ability, "physiological senescence", which is the topic of this text, regarding previous physical activity, specially exercising, can be divided into three types of elderly. The "older" elderly have the highest functional capability of 2–3 MET (MET=metabolic unit, i.e. the oxygen consumption of 3.5 ml/kg body mass in one minute), the "younger" older are the persons of older age having maximal functional capacity of 5–7 MET, while the "sport-s" elderly have the functional capacity of 9–10 MET, independently of chronological age. The majority of the above mentioned changes can be confirmed by the so-called non-invasive diagnostics, along with clinical examination, ECG, ergometry and echocardiogram. According to the data from our studies, over one third of people aged 65 and over has no signs of the described changes in regard to the mentioned parameters *(16)*.

The changes in *vascular system* can be numerous, and by some authors, could start to happen from the beginning of the fourth decade of life. Some changes are mentioned in a series: the quantity of collagen in the arterial walls is increasing and calcium is being deposited in collagen. The amount of elastic fibers is diminished; the inner layer-intima becomes more voluminous, permeated by altered smooth muscle cells. Arteries can become hard, elasticity is lost, what is particularly visible in the aorta. In veins the wall also becomes thicker, media fibrosis is present, veins could become twisted, especially those exposed to elevated pressure. Capillaries also change, basal membrane thickens, along with increasingly pronounced endothelial "fenestration". Due to increased peripheral vascular resistance, the organ perfusion can be reduced, less in skeletal muscles and myocardial muscle, and more in kidneys, mesenteric blood vessels, splanchnic vessels and skin. The result of this can be the elevation of mostly systolic arterial blood pressure, while for diastolic it is less pronounced *(6,14–18)*. Moreover, in the so-called advanced age diastolic pressure can be lower than in middle age. Activity of the autonomous nervous system is reduced, the neurotransmitter synthesis and the amount of receptors, as well as the sensitivity of baroreceptors. The plasma noradrenaline level can be increased. Often the process of atherosclerosis is intertwined in this. But atherosclerosis is an inflammatory disease, and not the consequence of advancing physiological age.

Respiratory system

The respiratory system, by some authors, can be also susceptible to changes with progressing age again from the fourth decade of life onwards. The number of cilia in respiratory pathways diminishes. Alveolar macrophage are less efficient, lung elasticity is decreased, sternocostal joints become inelastic, as well as the spine, which becomes spondylotic. The consequence is diminished chest expansion while breathing, causing greater work of muscles for removing the air from the lungs. The speed of expiratory air flow can be reduced, and alveolar-arterial oxygen difference grows. Decreased can be functions of dynamic respiratory volumes that can be evaluated by respirometry testing: forced expiratory volume ($FEV_{1.0}$), *FEV* (fast expiratory flow) $_{25–75\%}$, VC (vital capacity) $_{75–85\%}$, MV (maximal volume of breething), maximal expiratory flow, maximal minute ventilation., the highest breathing capacity *(6,16,19–21)*.

Functional residual capacity increases to 60%, in comparison to 50% in the so-called middle age. The consumption of energy needed in breathing is growing, and due to the aforementioned reduced minute heart output and increased peripheral vascular resistance, the possibility of microcirculation spreading can be reduced. The input of oxygen is lessened, arterial oxygen saturation is decreased. The 2, 3-diphosphoglycerate concentration is reduced, causing the change of the dissociation curve to the left. Regarding the acid-base status, the total buffer capacity is reduced in comparison to the so-called middle age, the bicarbonate level can be reduced. However, the excretion of carbonic acid does not change.

Kidneys

In kidneys of the elderly both functional and organic changes can develop. Firstly changes in blood vessels occur, leading to the alterations of nephron functions. The number of capillaries is thinning, influencing both glomerular and peritubular parts of the kidney. The total kidney weight can be reduced. The connective tissue is increasing and the basal membrane becomes thicker. Glomerular capillaries degenerate, and these parts are bridged by arterioles. Small arteries lose elastic tissue which is replaced by collagen tissue. Arcuate and interlobar arteries become coiled. The basal membrane of renal veins thickens, and this process starts from the fourth decade of age onwards. The amount of connective tissue increases. The hydration of renal medulla abates with aging, causing the diminished concentration ability of kidneys. The kidney weight from the fourth till the eight decade of life is reduced for about 30%. Renal blood perfusion can be diminished on average for about 10% per decade, starting with the fourth decade onwards, probably as the result of parenchymal and vascular changes, with simultaneous reduction in the cardiac output for more than a third. The renal perfusion in the ninth decade of life amounts to only about 60% of that in younger people. Partial renal functions weaken in senescence due to numerous reasons, for example, because of the loss of nephrons and changes in blood vessels, alterations in filtration and perfusion connected with the advancing age, and partly due to the reversible changes of tonus in glomerular blood vessels *(4, 6, 8, 11, 20, 21)*.

The endogenous creatinine clearance, as the result of glomerular filtration, can be reduced for 8 ml/min per decade on 1.73 m^2 of body surface, starting from the fourth decade onwards. With advancing age, proportionally with the reduction in glomerular filtration, muscle mass diminishes as well, so the reduction in glomerular filtration need not necessarily be accompanied by simultaneous rise of serum creatinine. But this change will be observable in the analysis of the endogenous creatinine clearance. Glomerular filtration at the age of 90 years can be reduced for about 50% in comparison to the age of 35. By some authors, the serum creatinine concentration of 124 μmol/L (1.4 mg/100 ml) is compatible with the reduction of glomerular filtration in the elderly for about one third. The normal values of creatinine clearance in these patients have been recorded in 20% of the cases.

These parameters could also serve in the evaluation of biological age. However, by our study, one third of elderly persons have renal function within normal range. The renal plasma flow can be reduced with advancing age. According to some data, in men aged 65 and over it is 420 ml/min (the normal value determined by the para-aminohippurate for men is 645±163 ml /min, and for women 594±102 ml /min), and at the age of 75 it amounts to 350 ml/min.

The kidneys of an elderly person cannot maintain an adequate acid-base balance in blood often. This is partly the consequence of reduced ability of kidneys to excrete ammonium, while phosphates somewhat increase due to the reduction of the proximal tubule reabsorption. Phosphates are capable to create "titratable acidity". The osmotic urine concentration diminishes with aging.

The maintenance of buffer systems within normal limits is performed by kidneys. All the three kidney functions change in old age: the regulation of bicarbonate quantity, excretion of hydrogen ions and the restoring of the buffer systems by the replacement of urine cation with the ammonium ion.

The regulation of water and salts in the organism depends on the excretion of both water and salts, and vice versa: their retention in the organism, according to the actual need. This depends on the vasopressin secretion (hypothalamic-hypophyseal mechanism), as well as on the aldosterone mechanism of the adrenal gland *(4, 6, 8, 11, 16, 19, 21)*.

It seems that age has not a particular influence upon the vasopressin secretion, but aldosterone has lower concentration in the elderly compared to younger persons. The distal tubule is less sensitive to vasopressin, and the osmotic capability of kidneys in an elderly person is reduced. The result of both phenomena is the weakened ability of maintaining water and salts in the organism. According to that, the processes of concentration and dilution in the elderly can be less efficacious than in the young.

Some parameters indicating functional changes of cardio-respiratory and kidney systems are presented in Table 2.

Skin and epidermal tissue

The skin changes with age. The germinative epidermal layer diminishes and the number of germination cells is reduced. Also, the number of sebaceous and sweat glands becomes smaller; the skin becomes thin, its elasticity is lost and it wrinkles, especially on the face. The epidermal fat tissue is reduced and the skin loses some of its thermal insulation properties *(4, 6, 11)*.

The quantity of subcutaneous tissue decreases, the skin itself becomes thinner, sweat glands undergo atrophy, and sweating is lower. The blood perfusion of the skin diminishes, both due to changes in blood vessels and to decrease in heart output. Thermoregulation changes, due to the above-mentioned factors, but also as a result of changes in the central nervous system. The result is a weakening of the ability to emit heat and to maintain body temperature.

Nails grow more slowly, they become blunt and yellowish, and the content of calcium declines. Hair is lost from the scalp, armpits and other places.

Supportive tissues

The supportive basis of the connective tissue changes and the water content reduces, while the amount of solid tissue grows. The latter consist of polymers condensing in old age. Collagen fibers become both larger and more

numerous, their fusibility decreases, and their structure becomes more solid. However, their mechanical properties become aggravated. Consequently, more strength is needed for adequate extension, while return to the initial length is slower. In very advanced age, however, the collagenase enzyme concentration is increased, causing less expressed collagen inelasticity. With age, elastin fibers lose water, become intense yellow, hard and stiff. This is especially observed in stress, when they break and become fragmented. They are sometimes replaced by collagen fibers. With advancing age emerges a substance with properties in between collagen and elastin – the so-called pseudo-elastin. Its structure comprises an amorphous substance sheath around collagen *(4, 6, 12, 16, 17)*.

The hyaline cartilage dehydrates through the years, and turns into fibro-cartilage. The joint cartilage becomes yellow, loses elastic properties, and in more mechanically loaded sites, e.g. the knee meniscus, it becomes thinner. The cartilage can completely "ossify" due to calcifications. The skin loses elasticity, the joints become stiffer due to fibrous tissue and the rib cartilages lose elasticity, and stiffen. The intervertebral discs harden due to the restricted water content.

Muscles

The muscle mass in men in so-called middle age, in some cross-sectional studies, is about 12 kg higher than at the age of about 65 years, and in middle aged women about 5 kg higher than at the age of 65 in comparison to ages 25. The pigment lipofuscin is accumulated in muscle cells (so-called the "aging pigment"), the quantity of fats increases, some of the muscle cells deteriorate and are replaced by connective tissue. An attempt to regenerate myocytes is the synthesis of proteins in their peripheral parts, lessening the ATP content, decreasing the ratio of ATP and ADP, and diminishing the quantity of glycogen and creatinine phosphates. Simultaneously, but to a lesser degree, motoneurons are being lost. The amount of spontaneous neurotransmitter release decreases, although membrane potentials do not change with advancing age. In some studies, working capacity i.e. use of large muscle groups over longer periods of time, in older age is approximately one third lower than that of middle aged persons *(4, 6, 17, 20, 21)*.

Bones

Bones also undergo numerous changes, particularly in women after menopause. The mineral content of bones subsides for about 10% with advancing age and the organic bone matrix. In long bones remodeling occurs. The outer bone diameter is increased, the bone mass becomes thinner and the resulting space is filled with fat and fibrous tissue. The bone cortex becomes thinner with the increasing inclination towards fractures. This loss of mineral content is particularly pronounced in women after menopause. Consequently, the frequency of bone fractures is several times greater in women than in men. Data show that each fifth woman aged about 80 yrs experiences the thigh-bone fracture. Many factors are responsible for that, from the imbalance of osteoblastic and osteoclastic activities (particularly in post-menopause) to the change in the relation of parathromones and calcitonin. The latter happens due to the changes in the estrogen quantity, because the calcitonin excretion is under direct influence of the estrogen rate in the blood flow. The consequence is the larger quantity of parathormone which directly influences the bones and the increased excretion of minerals through kidneys. Besides that, the decreased concentration of hydroxylated D3 vitamin is observed in the elderly, leading towards reduced calcium absorption through the small intestines membrane which causes an increased calcium release from the bones in order to achieve the adequate serum calcium level *(6, 12)*.

Teeth and oral cavity

By some studies, about the half of people at the age of 65 have no one teeth. The loss of teeth will of course, besides the chronological age, depend upon the mouth cavity hygiene, but also upon other concomitant diseases. Dentin decreases with age, odontoblasts increase their activity and degenerate, dentin becomes turbid and hypohydrated. The tooth pulp is almost filled in, partly by the altered odontoblasts. The amount of cemented substance is decreasing, and the changes in bones are characterized by the mineral loss and bone matrix resorption *(6, 19)*. Changes in blood vessels and nerves of the oral cavity occur as well, the blood flow through the salivary glands subsides, leading to the reduced mucin secretion. The tongue is prone to atrophy, while the sense of taste can be lost up to 70%.

Digestive system

The loss of teeth can be an important factor of malnutrition in old age, along with the reduced senses of taste and smell. In some studies even the connection between the number of missing teeth and decreased hemoglobin concentration in the serum can be found due to the reduced intake of proteins, caused by lost teeth. The salivary glands secretion and its volume can diminish. The esophagus *motility* is changing. The upper esophageal sphincter relaxes inducing a peristaltic wave. In normal conditions, the wave reaches the lower esophageal sphincter, which starts to relax enabling the food to pass freely. In the elderly, not every mouthful leads to the peristaltic esophageal wave, thus the lower sphincter does not open to each food passage. On the other hand, the total motor activity of the esophagus is not coordinated well, although the total motor function is intact. As each morsel does not incite the peristaltic wave and does not pass through, the elderly persons lose the wish for food. With advancing age, the pH value of the gastric juice increases, but the gastric secretion diminishes. Lessened is also the number of cells participating in the process of absorption, causing atrophic gastritis. The atrophic gastritis affects both the mucus and the muscle part. Hypochlorhydria or apochlorhydria are frequent. The elimination of gastric content slows down. The intestines motility is decreased, too. There is not enough evidence

that aging reduces the absorption of many foodstuffs, but the damages can be expected because the mucosal surface is reduced. Also, sufficient evidence is lacking to confirm that the amino-acid absorption in old age decreases, but the fat absorption is slower than normal. The consequence of the weakened absorption of secretin, amylase, trypsin and lipase in old age, probably due to the decrease in the last one, is the slower absorption of fats *(6, 16)*.

The small intestine diverticulosis and colonization can develop. The changes in the colon are constipation and diverticulosis. Constipation is helped by the restricted motor function of the colon, the weakened reflex of colon emptying, mostly reduced fluid intake, reduced intake of food containing fats, neurological diseases, as well as by some endocrine diseases, like hypothyreosis. Incontinence can also occur due to the loss in tonus of the inner and outer anal sphincters. Along with all the mentioned, the cardiac output reduces, thus the blood flow through the alimentary system is reduced, too. Mesenteric and splanchnic flows can be diminished as well, the later by about 40%.

Basal metabolism decreases with aging, body activity is often reduced. It is recommended to lessen the intake of calories for about 15% from the 45th till 65th year of life, and after than for 10% per decade. It is advisable to take larger quantities of vitamins A and B_1, because too small amounts of B group vitamins are usually taken, particularly of cyanocobalamine (vitamin B_{12}). Also, fibrous foodstuffs should be preferred in order to prevent constipation.

Liver

Microsomal liver activity diminishes with aging and thus increases the sensitivity for some drugs, e.g. barbiturates. The liver weight liver reduces as well as the blood flow though it. However, no proofs have been found for the reduction of biliary secretion, but gallstones are presented more frequent in older than in younger persons. According to some data, it is seen in 10% of elderly men and in 20% of older women. Histological changes in the liver observed in senescence are usually vacuolization and hepatocyte degeneration, the occurrence of fatty infiltration and reduction in liver glycogen *(6,11,16)*.

Elderly people often have hypoalbuminemia, both due to the reduced albumin synthesis in the liver and to albumin catabolism (albumins are synthesized into hepatocytes).

Blood and blood-producing organs

The amount of active bone marrow can be reduced with ageing, and this process particularly affects long bones, while in flat bones this change happens much more slowly, and in the vertebrae very slowly. The functional reserve of hematopoesis diminishes as well. However, the acute state, as the sudden loss of blood, can still be adequately compensated in old age. Erythrocytes in an elderly person are just a bit altered than in a young person. Their diameter increases with aging and they become more fragile. This may be in connection with the ability of the spleen and lymph tissue to remove old erythrocytes. The length of erythrocyte life in the elderly is the same as that in younger people: 120 days *(4, 6, 11, 16, 20)*.

TABLE 2

Parameters indicating changes of heart, lungs and kidneys (6, 9, 16).

Parameter	Changes in decade after 30 years
Stroke volume	–10%
Cardiac output	–7%
Peripheral vascular resistence	+12%
Working ability	–10%
Forced expiratory volume in the first second ($FEV_{1,0}$)	–320 ml
Forced vital capacity (FVC)	–250 ml
Creatinine clearance ml/min/1,73 m^2 of the body surface	–8

The blood volume in an older person is maintained within normal limits till the age of about 80 years, and after that it increases depending on the active cell mass. The number of erythrocytes and hematocrit values remain within normal limits up to the age of about 65 yrs, and then they can be gradually decreased. However, these are not the causes of anemia in older patients, but the most frequent reasons are a chronic disease, malnutrition and reduced mobility. Erythrocyte sedimentation rate can be increased with aging, probably due to the changed of the plasma proteins concentration.

The white blood count also shows changes in senescence. Granulocytes have fewer granules; lobulations and osmotic resistance are increased. The number of lymphocytes is reduced, while the number and function of thrombocytes do not change.

Fibrinogen can be elevated concentration in old age, for about 25%, albumins have reduced concentration, globulins somewhat higher, the quotient of albumins in regard to globulins is diminishing. High density lipoproteins do not alter in concentration, but the concentration of low density lipoproteins grows.

Immune system

The immune system efficacy can be diminished with aging. The occurrence of malignant and immune diseases or of bacterial, viral, fungal and other infections is a frequent phenomenon in elderly people. The tissue of lymph nodes, thymus, spleen and bone marrow change with advancing age. An immune response, according to some authors, is ten to twenty times lower in older age than in puberty. Thymus is the central part of this system, responsible for the immune changes in senescence. However, changes in this gland start already in childhood, and some authors call it “the time clock”. The immune system

changes are particularly observable in the alterations of T-lymphocytes, which are responsible for cell immunity. It is the main cause of changes in the humoral immunity. Thymus is needed for their creation from pre-T-lymphocytes. The result is a disproportion between enhancing and suppressive functions in older age. The changes in B-lymphocytes, responsible for humoral immunity, are less expressed than the changes in T-lymphocytes. Although the lymph tissue is susceptible to atrophic processes, in the adrenal glands core a hormone thymosin is being created up to a very advanced age, although in elderly people it is being generated more slowly and with lower concentration than in younger people. The connection between the hypothalamic-hypophyseal system and the immune system is shown in the fact that the growth hormone and insulin have an impact upon the T-lymphocyte function, while sex hormones and thyroxine affect both T- and B-lymphocytes. The immune changes as the reason for ageing, i.e. for the diseases more frequent in older than in younger persons, are still an open problem regarding their causes and consequences *(4, 6, 11, 16, 20)*.

The immunoglobuline concentration does not change much during aging. The serum IgA and IgG levels are increased and IgM level decreased with aging. The response of antibodies for foreign antigens are decreased. Autoantibodies could be detected more frequently in sera in the elderly.

Endocrine system

By some authors, the pituitary gland does not change in weight with higher age, but its blood saturation is reduced, and the amount of connective tissue is increased. The growth hormone remains unchanged as well as the corticotrophic hormone. However, the growth hormone's concentration in blood flow rises more slowly, like in the insulin stimulation, but those changes probably connected with obesity and not with aging. Prolactin concentration does not change as well, and its slower secretion is also provoked by stimulation tests. Vasopressin is the same or somewhat higher in older as in younger persons *(6, 16)*.

The adrenal gland diminishes with age, fibrous changes occur, and pigment is deposited in the cortex. Glucocorticoids concentration in the plasma of the elderly does not change, although the elderly have elevated concentrations, and the concentration of aldosterone can be lower than in younger ones.

The thyroid gland can be morphologically altering with age: the amount of colloids decreases, as well as the follicle diameters, but its function remains unchanged for a long time. Triiodothyronine (T3) loses its concentration with time, while the concentration of tetraiodothyronine (T4) does not change, but the conversion of T4 into T3 outside the thyroid gland is restricted. The quantity of the available T4 is reduced due to the subsided enzyme system in the liver. The TBG (thyroid binding globulin) concentration somewhat reduces with advancing age.

The parathyroid glands can be changed morphologically, and the amount of fat tissue in them grows. The circulatory quantity of parathormones in elderly women is double that that in elderly men, and with age their disintegration in kidneys falls off. This leads to osteoporosis.

The pancreas does not change in weight during aging. The serum insulin level in normal conditions remains unchanged, but the glucose tolerance can be weaker, as well as the pancreatic beta cells sensitivity. The concentration of glucagon also remains the same regardless of age.

Reproductive system

The testicles do not alter in weight during ageing, but the amount of intertubular connective tissue can be increased, and the basal membrane around seminiferous tubules thickened. Germinative cells, Sertoli's and Leydig's cells can be reduced in number, and the remaining ones have a lower content of lipids and restricted androgenic secretion. By some authors, in cross-sectional studies in the age group 60–70 yrs, about 70% of active spermatozoids remain, while this percentage decreases to 50% in the age group of 80–90 yrs *(6, 16)*.

The prostate gland can be more permeated with connective tissue in older age, acinuses are lost; it becomes larger and hypertrophic. The amount of androgens in urine is decreased and of gonadotrophin increased.

The ovaries can also present morphological changes. Oocytes are lost; the uterus loses weight, while the uterine tubes and vagina shrink. The breasts diminish and are replaced by connective tissue. The amount of estrogen in urine decreases, while the gonadotrophin concentration rises.

Central nervous system

The central nervous system can be changed with advancing biological age. Blood flow of the brain could be diminished because of atherosclerotic changes of blood vessels, i.e. carotid and vertebral arteries, the cardiac output is decreased, and all those changes could be reasons for neuronal loss. The blood flow through the brain, which is in normal conditions 50–60 ml/min/100 g tissue, with the advancing biological age can be reduced to about 40 ml/min/100 g tissue *(4, 6, 11, 20, 21)*. The brain weight changes on average for about 7% in comparison to younger age, i.e. for about 100 g. The loss of cortical brain tissue is more pronounced, sulci become broader, and gyri shallower. In some parts of the brain even up to 20–40% of cells are lost, particularly in the temporal gyrus and area striata. In the elderly we are facing with cell loss, which varies in different parts of the central nervous system. In some cells, particularly in hippocampus, vacuolar degeneration occurs. Neuroaxonal degeneration is also present, with the loss of myelin. In neuronal cells is accumulated the "aging pigment" lipofuscin. Although

the described changes do happen, a large number of authors consider that the reduction of the brain function in biologically higher age most often is not the consequence of biological senescence but of illness. Elderly people are susceptible for effect of drugs – all mentioned changes could be reasons for side effects of psychoactive and other drugs: ß blocking agents, Ca antagonists etc.

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