Jolanta Klusek, Justyna Klusek

Phenomenon of ageing – a process or a state

The problem of ageing is among the oldest research problems. Long ago in the 1st century B.C. Marcus Tullius Cicero said: "[…] when I reflect on this subject I find four reasons why old age appears to be unhappy:

- it withdraws us from active pursuits;
- it makes the body weaker;
- it deprives us of almost all physical pleasures;
- it is not far removed from death."

The considerations of Cicero concerning passing away and death still remain up to this day. Until today, despite the development of science, many questions concerning the ageing of the body remain unanswered. There has even developed a separate scientific domain dealing exclusively with the aging of organisms – gerontology. The term is derived from Greek: *geron* – meaning "old man" and *logos* – meaning "study" or "word".

Many researchers have attempted to suggest the definition of ageing. One of them defines ageing as progressing with the age of the body decline in its capabilities for self-repair of growing intracellular damages. There occurs a gradual extinguishing of life functions, this process cannot be avoided, although it may last for varying lengths of time. In Europe and the United States of North America, the average life span is 75 years, while in some regions of the world, e.g. in Georgia or the Andes, people can live up to 110–120 years. Therefore, the world population constantly increases. In 1950, it was 2.5 billion, in 2009 this number exceeded 6.7 billion, whereas the prognoses for 2050 show an increase up to 9 billion. It is an alarming fact that the elderly will constitute a considerable percentage. This is due to an increasingly more effective prophylaxis and a considerable decline in birth rate. The average life span increased from 45 years in 1900 up to 75 years at present. This growing number of the elderly poses a great challenge for the future. Together with age, there decreases not only the condition of the body, but also physical efficiency and cognitive functions. Ageing is also associated with an increased risk of so-called age-related diseases.

Thus, the elderly should be provided with appropriate care. The problem of ageing is no longer a scientific problem, but has also become a social problem. Therefore, it is very important to quickly and precisely recognize the causes and mechanisms of the process of ageing on all levels of biological organization of the body, starting with cellular structures, through the entire cell, tissues, and individual organs of all systems – the cells lose their replication potential, cease to divide and are ageing.

Ageing on the cell level

Since the 1960s, it has been known that cells are ageing, which was indicated by Leonard Hayflick and Paul Moorhead (1961) who confirmed that cells *in vitro*, although having undergone a specified number of divisions, cease to divide, but do not die. They lose their replication potential; however, for a long time they may preserve their metabolic activity.

During the process of ageing, the total number of cells within their populations decreases, which is clearly observed, e.g. among the cells of the central nervous system and in the population of liver cells – hepatocytes. In the ageing cells, a decrease is noted in capabilities for proliferation, e.g. among fibroblasts (Bayreuther et al., 1988; Norwood et al., 1990).

In the cellular membrane an increase in the concentration of cholesterol is observed accompanied by a simultaneous decrease in the content of phospholipids, resulting in an increase in stiffness and viscosity of membranes, a decrease in their flexibility which, in consequence, may lead not only to a decreased rate of lateral diffusion of plasma membrane components, but also a hindered flow of information signals to the cell. Such phenomena may be observed in enterocytes of the intestinal epithelium and epithelium of the prostate, as well as in the membranes of neurons, hepatocytes and cells of skeletal muscles, lipocytes and thrombocytes from older individuals (Viani et al., 1991; Wahnon et al., 1989; Watała, 1991; Wood, Schroeder, 1988; Yegutkin et al., 1991). In the cellular membrane a rapid decrease is noted in the amount of cell receptors, e.g. β-adrenergic receptors on the surface of neurons of the heart muscle cells (Roberts, Steinberg, 1986; Sprent et al., 1991).

In the ageing cells changes in the cytoplasm take place. Cells lose considerable amounts of water; therefore, the tissues become less flexible. This is most clearly observed in the skin, muscles, and blood vessels. Changes are observed in the fine structure of mitochondria. The density of their matrix decreases and the crista become shorter. These structural changes lead to functional changes, e.g. in old rats it was observed that mitochondria of the heart muscle cells are more sensitive to decreased oxygen pressure in breathing air than the mitochondria of the heart of young rats.

It is known that the most materially stable cell component is its DNA located in the nucleus. However, there are many environmental factors which may cause damage, such as radiation, or specific chemical substances. These lesions could be of permanent character if it was not for the capabilities for cell repair in the form

of specific enzymes, so-called polymerases. Together with age, the repair apparatus is subject to damage; therefore, the number of ruptures and damage to the DNA strand clearly increases, and a larger amount of damaged DNA stretches accumulate in the cell. This is especially clear in the nuclei of the cells of the brain, liver and heart. Many researchers presume that it is for this reason that old cells have smaller chances for survival due to the accumulation of damages and abnormalities in the DNA strand. Changes in the structure of DNA lead to errors in the replication of protein molecules. If the number of errors in translation exceeds the capabilities of the cell – which takes place at an older age – its death occurs due to structural and functional disorganization.

During ageing, not only the pace of DNA damage increases, but its interaction to chromatin proteins also changes. With age, the strength of DNA binding to these proteins increases by a change in the electrical charge of proteins, and as a result of water loss. The level of chromatin condensation changes, it becomes more dense, which hinders transcription.

The ageing of the body depends not only on changes taking place on the cell level. At present, there are many documented anatomical and physiological observations which describe changes in individual systems during the ageing of the body (Austad, 2012; Couteur et al., 2012; Lopez-Otin, 2012).

Nervous system

It seems that the consequences of ageing of the nervous system, and of the brain as the organ controlling the whole body, are especially important. With age, there occurs a decrease in brain mass, thickness of the cortical plates, as well as the amount of myelinated nerve fibres. For a long time, it has been considered that the ageing of the brain is associated with the death of neurons. Studies conducted in recent years have shown that physiological ageing does not lead to clear changes in the number of neurons in the brain (Morrison, Baxter, 2012; Pakkenberg, Gundersen, 1997; West et al., 1994). Nevertheless, clear changes are observed in the morphology of neurons. A decrease is observed in the volume of neuronal bodies, in the number of branches of dendrites, and a decrease in the number of dendric spines, which leads to decreased communication between neurons (Bertrand et al., 2011). In addition, a decrease is noted in the capabilities for neurogenesis (Morrison, Baxter, 2012). However, these changes are not equally intensified in all structures of the brain. The frontal lobes shrink most strongly, which may result in difficulties with concentration and decreased abilities for focusing attention on several things at the same time. The hippocampus, the structure engaged in learning and memory, is subject to especially big changes. Also in the cerebellum, a rapid decrease occurs in the number of Purkinje cells, which in older individuals causes difficulties with locomotion, maintenance of balance and proper body posture.

The effectiveness of receptors decreases, reaction time prolongs, and the speed of voluntary movements decreases. A decrease is noted not only in the number of

connections between nerve cells, but the changes also concern the sole motor plates. The endings of axons shorten and do not reach many receptors, the field of terminal branches considerably decreases, there occurs fragmentation of the connections, a decrease occurs in the number of synaptic vesicles and, consequently, a decrease in the amount of transmitters reaching the synaptic cleft during stimulation.

Endocrine system

With age, a gradual and irreversible deterioration is observed in the functioning of the endocrine system, which is considered to be responsible for the stimulation of changes associated with ageing. It starts to respond increasingly more weakly to changes in the environment, and the secretory activity of endocrine glands clearly decreases (Arlt, 2004; Chahal, Drake, 2007; Djahanbakhch, 2007; Midzak, 2009; Peeters, 2008). This is especially clearly observed in the example of testes in males and the level of testosterone in their blood. It is known that over 95% of testosterone is produced in the Laydig cells in testes. With age, the number of these cells decreases by more than 40% in males aged between 50–76. Characteristic changes are observed in their structure. There occur many vacuoles, lipofuxine grains accumulate, and the number of nuclei may even increase (Bilińska et al., 2009; Chen et al., 2009). In this way, the changed cells produce increasingly less testosterone. It was confirmed that between the ages of 55–68 of life, the level of testosterone decreases by 1.4% annually (Perheentupa, Huhtaniemi, 2009).

The ovaries are also subject to ageing processes, and over the years they produce increasingly less ovarian follicles. Simultaneously, there occur disturbances in the secretion of hormones. An increase is noted in the level of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in blood (Tatane et al., 2008; Djahanbakhch et al., 2007).

In older individuals, a very clear decrease is observed in the levels of oxytocin and vasopressin produced by the hypothalamic neurosecretory cells which flow via neurons to the posterior lobe of the pituitary gland, where they are stored.

It is an interesting fact that the secretion of thyroid gland hormones remains on a constant level throughout most of life. As late as over the age of 60 a decrease in hormones concentration is observed, but only of triiodothyronine (T_3), whereas the level of thyroxine usually remains unaltered. Changes also concern the sole thyroid gland. The degradation of the secretory epithelium, decrease in the volume of follicles and overgrowth of the connective tissue are only some of the changes exerting an effect on a decrease in the secretory function of the thyroid gland. The activity of parathyroid glands also changes, resulting in a decreased secretion of calcitonin, which leads to osteoporosis.

Over the years, the concentration of growth hormone somatotropin (GH) in the blood clearly decreases as a result of decreased secretion of samatoliberin and increased secretion of somatostatin (O'Connor, 1998). Toogood (1996) reported that the mean concentrations of somatotropin in individuals aged 65–85 are by half

lower than in young people. In old individuals, the adrenal glands, especially their cortex, behave in an interesting way. The reticular and glomerular layers may disappear, while the fascicular layer increases. Also, the function of adrenal glands changes with age because of a decrease in the synthesis of adrenal androgens, whereas the synthesis of cortisol does not change. Similarly, for many years, much attention has been devoted to the role of dehydroepiandrosterone (DHEA) in the body. This hormone, synthesized in the reticular layer of the adrenal cortex, has been called by some researchers a "hormone of youth", because it was presumed to play a key role in the ageing process (Allolio, Arlt, 2002; Baulieu, 1996). Dehydroepiandrosterone belongs to neurosteroids, i.e. steroids synthetized directly within the central nervous system, which exert a modulatory effect on nerve conduction (Baulieu, 1998). From among all the steroid hormones, DHEA shows the highest concentration in blood: 10–15 times higher than cortisol, 100–500 higher than testosterone, and as many as 1,000–10,000 times higher than estradiol (Allolio, Arlt, 2002; Kroboth et al., 1999). The level of DHEA shows clear age-related differences. The peak values are manifested at the ages between 25–35; subsequently, these values considerably decrease and at the age 60–70 they are only 10–20% of the value occurring in 30-year--olds (Belanger et al., 1994). It has even been suggested that the concentration of DHEA may be considered as a marker of physiological ageing (Dharia, Parker, 2004; Yen, 2001).

According to the latest theory, melatonin, the level of which begins to decline from the age of 40, is considered as a hormone preventing ageing. A decrease in the secretion of melatonin by the pineal gland may be the result of the accumulation of calcium deposits in the pinealocytes, as well as a decrease in the number of β-adrenergic receptors on the surface of their membranes (Hadley, Levine, 2007; Karasek, 2007). The inhibitory effect of melatonin on the development of senile changes in various organs results from its antioxidative, free radicals sweep off properties, and anti-stress action, because the accumulation of lesions caused by free radicals is considered as one of the causes of the process of ageing of organisms.

Cardiovascular system

The process of ageing leads to structural, functional and biochemical changes in the cardiovascular system. Changes taking place in blood vessels concern the endothelium of the vessels. An impairment of metalloproteinase and angiotensin activity, an increased collagen synthesis, accumulation of cholesterol and lipoproteins deposits, lead to a decrease in the number of elastic fibres, and intensification of the processes of fibrillation and calcification (Rajzer, 2003; Rajzer, Kawecka-Jaszcz, 2007). Blood vessel walls are subject to thickening and subsequent narrowing, resulting in a decrease in their lumen, which makes them stiffer. The effect of considerably decreased susceptibility of large arterial vessels are primarily age-related changes in arterial pressure, leading to an increased aortic pulse wave velocity, resulting directly in an increase in systolic pressure (Graham, 2007; Kocemba, 1998).

The majority of changes taking place in the heart are related with the state of blood vessels; the heart must now overcome a higher resistance to blood flow, which causes a great loss of energy during the contractions of the heart muscle. The amount of blood pushed by the left ventricle into the aorta decreases, resulting in a smaller number of heart contractions. The time is prolonged in which blood fills the atria of the heart, reaches the lungs and other parts of the body, and the stroke volume also decreases. The changes taking place in the heart are of a morphological and functional character. As a result of apoptosis and necrosis, the number of cardiocytes decreases, which leads to an overgrowth of the remainder. Stimulated cadiomyocytes capture a smaller amount of calcium, which results in a decreased capability of the heart for systole and prolongation of the time of diastole (Siddiqi, Sussman, 2013). Depositions of amyloid and lipofuscin in the heart muscle lead to an increase in the thickness of its walls and loss of flexibility (Besse et al., 1994). In the cardiac stimulation-conduction system a decrease occurs in the number of peacemaker cells in the sinoatrial node, while the remaining structures are subject to calcification. Subsequently, there occurs disorder in the electrical activity of the heart (Sungha, 2007).

Muscular system

Analysis of the structure and function of skeletal muscles indicates that a relative stability of their development takes place as late as at the age of 20. Over the years, there occurs a loss of muscle mass (sarcopenia), and an accompanying loss of muscle strength (dynapenia). These are typical symptoms of ageing of the body.

It is known that a motor unit is the basic functional element of the skeletal muscles. It is composed of muscle fibres innervated by axon terminals of the same motor neuron, i.e. motoneuron. In the process of ageing of muscles there participate neurogenic and myogenic factors. Many reports indicate that the most important factor leading to sarcopenia is a gradual degradation of the nervous system supplying muscles. There occurs a loss of α-motoneurons, resulting in a loss of motor units. This process manifests at the age of over 60. It was found that between the ages 20–90 in the lumbar region of the spinal cord, approximately 25% of motoneurons disappear. The loss of motoneurons has very serious consequences. It leads to the demyelination of axons, which is associated with a decrease in the number and diameter of axons innervating the muscle. The loss of the myelin sheath and decrease in the diameter of axons lead to a decreased conduction velocity in all fibres of motoneurons. These changes in muscles innervation exert an important effect on their activity. In older individuals, a decrease is observed in the excitability of muscles, decreased lability, i.e. the number of responses to stimuli per second, chronaxie is prolonged – time of muscle response to a stimuli. In certain periods of ageing, the thickness of muscle fibre decreases. According to Wolański (2005) the diameter of the fibres of the thoracic muscle in an individual aged 50 ranges within

20–25 μm, at the age of 70 it decreases to 20 μm, while at the age of 80 it is only 10 μm. The loss of muscle mass and velocity of shortening of muscle fibres are the main cause of a decrease in muscle strength. It has been confirmed that between the ages of 50–70, muscle strength is reduced by approximately 15% per decade, compared to the strength observed in young people. After exceeding the age of 70, the loss of muscle strength is about 40%, whereas at the age of 90 muscle strength is by as much as 50% lower, compared to young individuals. Interesting changes are observed in the sole myocytes. In the sarcoplasm there occurs a considerable amount of so-called fatty vacuoles, which replace the disappearing contractile fibrils. There are several causes of the degradation of myofibrils – lack of stimulation on the part of the nervous system, deteriorating blood supply, and a decrease in the efficacy of mitochondria. Fatty vacuoles cause disorder in the course of contractile fibrils. Myofibrils, which to-date have been ordered parallel with respect to each other, begin to separate from one another and take a skew or spiral form, which considerably decreases the strength of contraction. In the muscle cell, a decrease is observed in the intracellular concentration of Ca^{2+} (Safrey, 2014), disorders in the synthesis of actin and myosin (Gannon et al., 2009), and an increase in the synthesis of myostatin – a protein important in the pathogenesis of sarcopenia, limiting muscles development (Baumann et al., 2013). In addition, these cells have a limited capability for glucose uptake and oxygenation. In these cells, a decrease is observed in the efficiency of the process of β-oxidation of fatty acids, there also occurs the accumulation of mitochondrial protein carbonyls and a decrease in the production of ATP, which leads to disorders in the process of cellular respiration (Demontis et al., 2013; Nehlin et al., 2011).

Immune system

During the ageing process there also occurs impairment of the immune system. The most important change in the functioning of the immune system of an ageing body is a gradual thymic involution. However, the cessation of its biological activity, leading to a decrease in the production of T lymphocytes, is not associated with a considerable decrease in immunity, because the body develops well in advance a sufficiently large population of T cells (Weksler, Szabo, 2000). Thus, with aging, no decrease is observed in the overall number of lymphocytes; however, there is a change in proportions between individual groups of these cells and their activity in the organism, which delays the process of formation of humoral and cellular response (Vallejo et al., 1998). There occurs a decrease in the capability of B lymphocytes for the production of natural antibodies, while the production of antibodies against own proteins becomes intensified. Thus, the effect of impaired functioning of the immune system is attacking the body's own cells by lymphocytes, the process called autoimmunoaggression.

Contrary to common opinion that ageing is the time following maturity, the process of ageing of the body starts at the very beginning of the life of an organism

and, according to many factors, takes place at a varied pace. The speed and pace of ageing depends, to a large extent, on the genetic factor determining the duration of life. External factors also exert an effect on the speed of ageing, such as: inadequate nutrition and inappropriate life style, past diseases, contaminated, ecologically devastated environment, and work in hazardous conditions (mining, metallurgy). It is obvious that this process is inevitable and irreversible. Attempts to halt or reverse the ageing process have accompanied humanity from the dawn of time. Unfortunately, together with the development of knowledge, dreams about longevity become increasingly more distant.

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Abstract

Ageing is defined as decline in organism's capabilities for self-repair of growing intracellular damages progressing with the age of the body. There occurs a gradual extinguishing of life functions. This process cannot be avoided, although it may last for varying lengths of time. The problem of ageing is no longer a scientific problem, but has also become a social problem. Therefore, it is very important to quickly and precisely recognize the causes and mechanisms of the process of ageing on all levels of biological organization of the body, starting with cellular structures, through the entire cell, tissues, and individual organs of all systems – the cells lose their replication potential, cease to divide and are ageing.

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Dr hab. prof. UJK Jolanta Klusek
    Institute of Biology
    Jan Kochanowski University, Kielce, Poland
    e-mail: j.klusek@ujk.edu.pl

Dr Justyna Klusek
    Department of Surgery and Surgical Nursing with Research Laboratory
    Institute of Nursing and Obstetrics
    Jan Kochanowski University, Kielce, Poland
    e-mail: justynaklusek@tlen.pl