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Healthy human aging: intrinsic and environmental factors

Envelhecimento humano saudável: fatores intrínsecos e ambientais

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Abstract

This review is an attempt to compile current knowledge on concepts and transformations that occur naturally in the human body and that characterize what is defined today as biological aging with quality of life and longevity. Many authors define natural aging as a continuous and uninterrupted process, which occurs in the human body causing structural and functional changes, classified as: cumulative, progressive, intrinsic and deleterious (CUPID). Usually these changes begin early in life and culminate in physical death. Genetic, chemical and biochemical changes lead to progressive degeneration of cells, tissues and organs, body systems and the organism as a whole, leading to loss of structures and functions due to aging. All these changes were discussed in some detail in the review here presented. We concluded that aging is not genetically determined, resulting in the accumulation of cellular and tissue damage, particularly in chromatin and DNA within cells, in addition to structural and bioactive proteins that command the general metabolism. Environmental factors such as feeding (nutrition) and lifestyle were also discussed.

Keywords: *Biological aging; CUPID; Natural aging; Progressive degeneration.*

Resumo

Esta revisão é uma tentativa de compilação do conhecimento atual sobre conceitos e transformações que ocorrem naturalmente no corpo humano e que caracterizam o que se define, hoje, como envelhecimento biológico saudável, com qualidade de vida e longevidade. Vários autores definem envelhecimento natural como um processo contínuo e ininterrupto, que ocorre no corpo humano provocando mudanças estruturais e funcionais, qualificadas como cumulativas, progressivas, intrínsecas e deletérias (CUPID). Normalmente, essas alterações começam muito cedo na vida e culminam na morte física. Mudanças de natureza genética, química e bioquímica conduzem a degradações progressivas das células, dos tecidos e órgãos, dos sistemas e do organismo como um todo, promovendo, com a idade, perdas de estruturas e funções. Todas estas alterações foram discutidas, em algum detalhe, ao longo da revisão apresentada. Concluiu-se que o envelhecimento não é geneticamente programado, resultando no acúmulo de danos celulares e teciduais, particularmente na cromatina e no DNA, no interior das células, e nas proteínas estruturais e bioativas, que comandam o metabolismo geral. Fatores ambientais, como alimentação (nutrição) e estilo de vida, também foram discutidos.

Palavras-chave: *Idade biológica; CUPID; Idade natural; Degeneração progressiva.*

1 Introduction and concepts

Biologists have usually tried to explain the aging process as general biological phenomena, which were under intense study or that seemed the most important at the time. Much of the current progress in genetics, evolution, and biology has been integrative, in part because many aging-related phenomena are considered now as multicausal. Therefore, it is necessary to formulate a synthesis of ideas that expand our understanding of the processes that are simultaneously and significantly rooted in each of these disciplines. These integrative approaches have necessarily led many people to be more receptive to

the study of interactions implied in aging. The process was easier because of huge amounts of empirical data on aging organized in meaningful and accessible review papers and symposia. As a result, the divisions between gerontology and other fields of biology are gradually being extinguished by the understanding that all parts of the life cycle are continuous in the process and in the mechanism, or else in the details. An important advance was the explicit acknowledgement that every human being follows the same path of growth, development, maturity and senescence, but differently.

2 Concept of aging and senescence

Some authors have similarly defined the aging and/or senescence process, but differently in content. Rothstein (1982) affirmed that aging comprises "changes from maturity to senescence". On the other hand, Strehler (1982) suggested that the fundamental age-related changes shall comply with the following conditions: 1) they must be deleterious, i.e., must impair functions; 2) they must be progressive, i.e., must occur gradually; 3) must be intrinsic, i.e., must not be the result of a modifiable environmental agent; 4) must be universal, i.e., all members of a given species must present this gradual deficit with aging. More recently, Masoro (1995) proposed that aging refers to "[...] degenerative changes over time, during the post-maturity life, increasing vulnerability to challenge and diminishing, therefore, the ability to survive". This definition is similar to Strehler's (1982), however not everyone would agree with the inclusion of time in a definition of aging. We know of individuals with the same chronological age, but who have quite different physiological ages. Therefore, time cannot be considered a default marker for all individuals. The time variable, however, determines the stages of life.

Arking and Dudas (1989) showed that a more sophisticated understanding of "aging" had been achieved, since time is only an imperfect analogous of the physiological processes in the course of life until senescence. We should be able to use the alteration in physiological variables instead of using the calendar to measure aging. This objective was achieved in a few experimental systems, including human beings (MANTON et al., 1995).

For these reasons Finch (1990) had already rejected the use of the word "aging" because of inappropriate connections with the idea of time as a dependent variable. The author has published a great book on this subject without even using the word *time*. Finch (1990) preferred the word "senescence", which he defines as: "age-related changes that affect adversely the vitality and the function of an organism, and above all, increase mortality rate in the course of life. Senility is the final stage of senescence, when the risk of mortality approaches 100%.

Senescence was defined by Strehler (1982) as "[...] changes that commonly occur in the post-reproductive period, resulting in decreased survival capacity of individual organism". Therefore, senescent changes occur mostly during late life and are associated partly with increased mortality, a characteristic of the last stage of life. "Aging" and "senescence" seem to be identical and the differences may be in emphasis rather than in concept.

It is worth to emphasize some of the concepts comprised in definitions presented by the abovementioned authors: 1) Not all changes occurring over time should be automatically considered as fundamental changes related to age. Time should be an independent variable; 2) Age-related changes usually begin to manifest during reproductive maturity, though its genesis might be traced to an earlier period; 3) Age-related changes are deleterious, progressive and cumulative. The organism's natural death is the endpoint of aging. It is an unexpected and sharp transformation from one state to another, even if the aging process progressively increases the probability of dying; 4) Aging and senescence are fundamental and intrinsic properties of most living organisms.

As a result of this point of view, one may define natural and healthy aging as a series of structural and functional changes independent of time; these changes are cumulative, progressive, intrinsic and deleterious, which usually begin to manifest in reproductive maturity and finally end in death. A simple mnemonic method to memorize this concept is the abbreviation CUPID (cumulative, progressive, intrinsic, deleterious). Age-related changes are not universal within the same species; different individuals may grow old in different ways. The best approach is to use always the criteria (CUPID) as a general rule and resolve questionable cases based on the available evidence. It is difficult but essential to define aging. Arking in his book "Biology of aging" after having reviewed other definitions states that biological aging is better defined by the abbreviation "CUPID", whose meaning has already been explained (ARKING, 2008).

Aging is a complex process (multifactorial), both at population and individual levels. Not all members of a population age equally; nor an individual's organs and tissues age at the same rate. The lifetime is a plastic phenotype, as evidenced by data organization in three organic patterns of senescence (quick, gradual and insignificant). Although real differences between species should be properly considered, a comparative approach of the biology of aging will tell which physiological systems and which organizational patterns may enlighten us about human aging.

3 Human aging

3.1 Human mortality and longevity

The ancient Egyptians established the maximum lifespan in humans as 110 years Smith (1993), which is not far from the current estimate of 121 years. Latest research shows that during the 20th century the average life

expectancy for women increased approximately 40% (58 to 81 years), whereas the average life expectancy for both sexes combined increased approximately 50%, from 50 to 75 years (SMITH, 1993). This progress was unequal in the demographic sense. Developing and poor countries are behind developed countries in almost 150 years. Such difference strengthens the remark that longevity depends upon the social environment in which people live.

As stated above, aging is characterezed by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. This deterioration is the primary risk factor for major human pathologies, including, cancer, diabetes, cardiovascular disordes, and neurodegenerative diseases. Aging research has experienced an unprecedented advance over recent years particularly with the discovy that rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution.

In a recent leading edge review, López-Otin et al. (2013), enumerates nine tentative hallmarks that represent common denominators of aging in different organisms, with special emphasis on mammalian aging. These hallmarks are: 1) genomic instability; 2) telomere attrition; 3) epigenic alterations; 4) loss of prosteostasis; 5) deregulated nutrient sensing; 6) mitochondrial dysfunction; 7) cellular senescence; 8) stem cell exhaustion and; 9) altered intercellular communication. We will come back on some of these alteration later on in this article. In this same line of investigation, Pivetta and Zorzetto (2017) also presents interesting investigations done in Brazilians Institutions and abroad.

4 Age-related changes (normal changes)

4.1 General anatomical changes

Changes considered normal occur in the course of time at skeletal, weight of internal organs and general composition at organism levels. Many body dimension indexes change at different age groups for different individuals and ethnic groups shown in Table 1 (ROSSMAN, 1977). This heterogeneity in growing patterns is not confined to the skeletal system and may also affect major internal organs, as shown in Figure 1 (ROSSMAN, 1979). There is not a simple and unique pattern of “normal” growth that is probably related to the normal functioning of each organ.

Following these changes in size and weight, there are changes in body composition. We literally become different people when we get older. Body fat increases with age both in absolute and relative terms. Such increase in body fat is followed by decreases in cellular solids, minerals and water. These changes are in agreement with longitudinal, transversal and cross-cultural data, which demonstrate we all are subject to changes in body composition. Comparing centesimal composition in men 25 and 70 years old (FRYER, 1962) we obtained the following values, respectively: fat, 14% and 30%; water, 61% and 53%; cellular solids, 19% and 12%; and bone mineral, 6% and 5%. Relative decreases of water and

Table 1. Changes in anatomical measures and indexes (probably due to aging) in years.

Measures	Anatomical Indexes
Weight	Increase until 50 and reduction from 60 onwards
Thoracic index	Increase from 34-40; reduction from 40 onwards
Biacromial diameter	Increase from 35-39; reduction from 55 onwards
Chest width	Increase from 50-54
Depth of the chest	Increase from 50-54
Sitting height	Increase from 35-39; subsequent reduction
Head circumference	Increase from 35-39; reduction from 54 onwards
Head length	Increase from 50-54
Head width	Increase until 40; slight subsequent decrease
Cephalic and facial indexes	Increase from 75-79
Total facial height	Increase from 30-34; subsequent reduction
Facial index	Increase from 25-29; subsequent reduction
Upper face index	Increase from 30-34; reduction from 55 onwards
Nasal height	Increase from 55-59
Nasal width	Increased in all age groups with age

Source: Adapted from Rossman (1977).

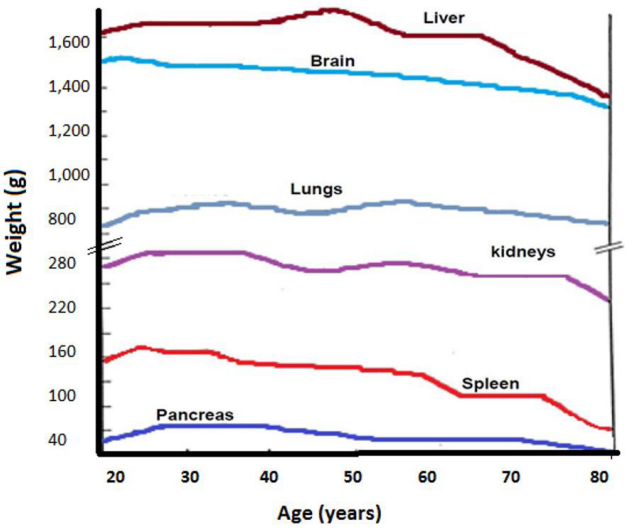

Figure 1. Changes in major organs weight with aging. Source: Rossman (1979).

cellular solids denote loss of muscle tissue, decrease of bone mineral denotes loss of bone mass, and the increase of fat content denotes greater proportions of adipose tissue in older people and decreased specific weight.

4.2 Structural and functional changes: organs and systems

The aging process affects multiple functions, organs and systems (Table 2). Decline in organ and tissue function may impair the nutritional status and its intervention (JENSEN et al., 2001).

Table 2. Aging effects on physiological systems.

Physiological system	Aging effect
Skin	Dry
	Wrinkling
	Excessive pigmentation
	Loss of elasticity
	Dilated capillaries
Oropharyngeal	Poor dentition
	Xerostomia (reduced salivary flow)
	Distortion of the sense of taste
	Reduced olfactory discrimination)
Gastrointestinal	Esophagus: motility disorders
	Stomach: delayed emptying
	Small intestine: intact structure and function
	Colon and rectum: constipation and incontinence
Cardiovascular	Thickening of the heart wall
	Increased collagen and stiffness of the large arteries
	Different opinions on the effect of the heart size
Pulmonary	Tissue stiffening
	Reduced vital capacity
	Decrease of maximal oxygen consumption
	Reduced respiratory capacity
	Reduced glomerular filtration rate
	Reduced renal blood flow
	Decrease in urinary creatine excretion
	Low sodium levels
	Reduction in renal concentrating capacity
Endocrine	Changes in the circulating hormone levels and their actions
Nervous	Reduced sensory perception
	Reduced muscle response to stimuli
	Loss of cognitive function and memory
	Brain cell loss

Source: Adapted from Jensen et al. (2001).

4.2.1 Skin and connective tissue

The skin is the human body's largest organ – approximately 16% of body weight according to Bloom and Fawcett, (1968), particularly if compared with the liver, which is considered a large organ – only 2-3% of body weight. It is the limit of the body and it helps maintaining the physical integrity. It is composed of an outer layer (epidermis), an intermediate layer (dermis) and a lowermost layer (hypodermis).

Normal age-related changes in human skin have been described by Kligman et al. (1985). The epidermis does not become thinner with aging. There is a marked decrease, however, in the density of the dermal papillae. These small protrusions of the dermis into the epidermis keep them tightly connected. On the other hand, the dermis does become thinner with aging. This thinning is associated with the change in the interlacing of collagen fibers in the dermis, resulting in less collagen per unit of the surface area. The net effect of these changes is looser skin that is more prone to wrinkle. Microvascularization also changes with aging; the capillaries and venules in the dermis and hypodermis become very sparse and irregular. The atrophy of the hypodermis is one of the factors that make it harder for older people to modulate heat loss. This atrophy is not a general phenomenon that occurs in the whole body, however it usually occurs in the face and in the back of the hand, not in the waist nor in the thighs (KLIGMAN et al., 1985).

For being the human body's frontier, the skin is affected by both intrinsic and extrinsic factors. Intrinsic changes include decreased density of dermal papillae, which leads to a loosening of the connection between the epidermis and the dermis. Changes in the type, structure and density of collagen and elastin fibers occurs constantly in the dermis. Actinic damage, caused by overexposure to the sun, accelerates and amplify these changes. The net effect of these changes is looser skin that is more prone to wrinkle. The loss of adipose tissue in the hypoderm and the microvasculature increasingly sparse and exhausted are two age-related factors that affect the regulation of heat loss.

4.2.2 Skeletal system

Cartilage and bone are specialized connective tissues that comprise the skeletal system. Each of these tissues consist of cells and fibers, e.g., collagen and elastin, inlaid in a non-living matrix produced and secreted by cells. Both the quantity and the rigidity of this matrix differentiate these hard skeletal tissues from "soft" muscles. Living cells are isolated in small cavities within the matrix, both in the cartilage and in the bone, and the majority of the tissue is composed of the matrix. Cartilage is capable of very fast growth and its matrix gives a considerable amount of rigidity. These two properties together (fast growth and rigidity) make the cartilage a

quite useful skeletal component, particularly for the embryo, in which the whole skeleton is formed first in a model of cartilage that only later is replaced by the bone. It is also useful for developing bones of young individuals and, lastly, for bone joints and articulation of adults. Cartilage is not an inert tissue because of its development in bone growth, but a rather invisible indicator of several metabolic disorders, such as nutritional or hormone deficiencies (BLOOM; FAWCETT, 1968).

With ageing the cartilage loses its translucency. The typical bluish colour of young adults cartilage changes until they become 20 years old to a yellowish opaque color. Fractures and wear of cartilage joints surface begin at around 30 years old. Although the old cartilage keeps producing the matrix, rates of synthesis decreases and the types of fibrils in the matrix change (TONNA, 1997). Calcification is the most important regressive change, in which small grains of inorganic calcium build up and the cartilage becomes hard and brittle. This calcification of the matrix affects the diffusion of nutrients and waste products within the cell or to another cartilage cell, resulting in cell death. With cell death the calcified matrix is slowly absorbed (LESSON; LEESON, 1970). Calcification and resorption is a normal part of the phenomenon in which the cartilage is transformed into bone, or in which broken bones heal. Besides collagen and elastin, it is known today that the main component of the collagen matrix is a protein molecule of high-molecular-weight with a complex structure called proteoglycan. Many chondroitin sulfate molecules are attached to it. Chondroitin sulfate electrostatically binds large volumes of water to the proteoglycan molecule, and this hydrated structure accounts for the resiliency of young cartilage (CAPLAN et al., 1983).

Bone mineral content increases during growth and development, reaching a maximum of 65% of the bone dry weight in healthy adults. Individuals with rickets or other bone disorders may have bone mineral content reduced to 35% (BLOOM; FAWCETT, 1968). Bone cells, called osteoblasts, are cells that form new bone tissue and are found in the surface of developing bones. Morphologically different cells, called osteoclasts, are closely associated with the process of bone resorption. Osteoclasts are often found in small depressions in the bone surface, in cavities caused by bone erosion around the cell. Bone remodeling begins during the fetal period, accelerates until it reaches its maximum for childhood and minority, continuing throughout the adult life at a very low level (RIGGS; MELTON, 1986).

Despite the apparent difference between them, today osteoblasts and osteoclasts are considered just different functional states of the same cell type. If one day there is an understanding of how to direct specifically a reversible modulation of cell activity, it will be possible to cancel osteoporosis, the major age-related change in the bone.

4.2.3 Muscle tissue

Muscles and bones give shape and delineate the human body. There are three different types of muscle: 1) skeletal or voluntary muscle; 2) cardiac muscle; and 3) smooth or involuntary muscle. Every bundle of muscle is made up of muscle fibers that are in turn composed of individual muscle cells connected to one another. The nucleus of the muscle cells is found on the periphery of the muscle structure and may be seen as the basic unit of organization of the muscle. In turn, the muscle fiber is made up of many myofibrils. Myofibrils have a very regular and periodic structure, based on the arrangement of two different families of protein molecules: actins and myosins. This organized molecular arrangement is what gives the periodic or striated appearance to skeletal muscle fiber and gives the muscle the ability to contract. Each of these repeating sections of muscle fibers is called sarcomere. Since the muscle is made up of sarcomeres repeated lengthwise, the muscle contracts by shortening the cumulative total of all sarcomeres, as shown in Figure 2. Muscle contraction is triggered by a nerve impulse released by the motor nerves to the individual muscle fibers. Although muscle fibers seem to have the same physical structure, it is possible to divide them in two different physiological types, depending on their innervation and contraction speed: fast-twitch and slow-twitch. The two types of fiber also differ in their genetic aspect. Duchenne muscular dystrophy is a disorder caused by a gender-related gene, which leads to skeletal muscle weakness. The genetic disorder that causes this condition is the absence of the protein dystrophin of a population of fast-twitch cells (WEBSTER et al., 1988). Older people usually have less muscle mass than younger individuals. This muscle atrophy is said to be caused by the decreased number and size of muscle fibers. Fast-twitch fibers atrophy because its nerves die. The fibers apparently cannot exist without innervation and when they die, they cannot be replaced. In human beings, the skeletal muscle is a tissue whose cells do not have divisions. The number of muscle cells is fixed in fetal development and the number of muscle cells formed remains throughout life. It is known, however, that physical exercise stimulates skeletal muscle growth, increasing the number of existing muscle fibers. On the other hand, lack of use, poor nutrition or denervation lead to muscle atrophy. It has been suggested that induced hypertrophy in fibers by physical exercise also causes a new innervation of muscle fibers, which compensates for atrophied fibers (WHITBOURNE, 1985).

Since muscle action is transmitted through tendons and ligaments, the conclusion was that some of the aging effects on muscle performance originated from age-related changes in these connective tissues. Older people are especially vulnerable to tendon ruptures, largely due to the loss of elastic tissue and changes in the

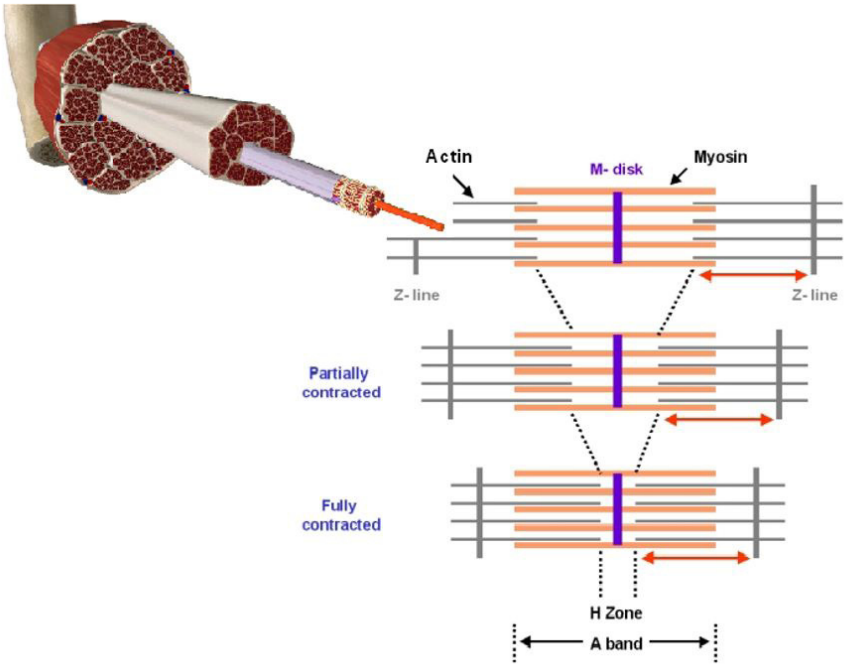

Figure 2. Diagram representation of the variation in sarcomere length: thin filaments (actin) slide past thick filaments (myosin). Source: Based on Barrett et al. (1986).

structure of the collagen, which reduce the tendon ability to stretch (SHEPHARD, 1982). The aging of collagen is characterized by progressive insolubility in various reagents, by increased chemical stabilization and by increased rigidity. There are reasons to believe that the age-related changes in tendons and in ligaments also affect muscle performance. These changes may result from cross-links between molecules of the connective tissue, an intrinsic process that may be modulated by extrinsic factors, e.g., diet and physical exercise.

4.2.4 Cardiovascular system

The cardiovascular system (CVS) has an important role of transporting nutrients to and carrying waste materials away from body tissues to the appropriate excretory organs. The CVS consists of a muscle pump (the heart) and two continuous systems of tubular vessels: pulmonary circulation and systemic circulation. Pulmonary circulation carries the blood from the lungs to the heart and back to the lungs; systemic circulation carries the blood to all organs and tissues of the body. In both circulations blood is pumped from the heart, passes successively through large and smaller arteries, capillaries, large and smaller veins and back to the heart. The nutrients and waste products are exchanged primarily in the network of capillaries in each circulation. Many organs are also supplied with lymphatic capillaries, which collect fluids lost by diffusion of blood during its passage through the capillaries, and return them to the blood flow. During this return, bodily fluids pass through a series of lymph nodes where the immune system can detect strange invaders in the lymph fluid.

The simplest vessel is the capillary composed of a single layer of endothelial cells (specialized epithelial cells). Endothelial cells also form the linings of the arteries, the veins and the heart. They provide a continuous lining through the CVS. Capillaries and their support cells in the brain seem to actively inhibit the transport of many molecules outside the vascular system and into the nervous system. This inhibitory function originated the concept of blood-brain barrier. During its relaxation phase (diastole), the heart actively expands, in part because of a mechanical recoil action attributable to the arrangement of connective tissue in the heart. This recoil action creates suction and helps to draw blood into the ventricles (ROBINSON et al., 1986). One of the major changes that can be observed with aging is the increase in coronary artery disease. Many studies suggest that approximately half of the elderly population has symptoms of cardiovascular disease. Epithelial cells in the intima (inner layer) become more irregular in size and shape. Muscular, elastic and smooth layers of the intima dramatically increase up to 40% in the aorta with aging. In the thoracic aorta this thickening is due to increase of the elastic layer; in the abdominal aorta it is due to the proliferation of smooth muscle cells.

In the heart, the only genuine and age-related change is an increase by approximately 30% in left ventricular wall thickness, caused by hypertrophy rather than hyperplasia (HANGARTNER et al., 1985). Cardiac muscle cells do not

have the ability to divide, they are post-mitotic cells that should last throughout the individual's life. It would be expected that such stable cells demonstrate progressive morphological and/or chemical alterations, which would reveal age-related changes. In fact, one of these changes that is well characterized is increased cardiac lipofuscin pigment according to age (KOHN, 1977). Most cardiac functions at rest do not demonstrate any age-related change, except for systolic blood pressure. Left ventricular wall hypertrophy can be interpreted as an adaptive response of the heart muscle to increased load on the heart.

4.2.5 Respiratory system

Branched airways are the main pulmonary system components, namely, the nasal cavity, pharynx, trachea, primary, secondary and tertiary bronchi, bronchioles, and alveoli. Bronchi, bronchioles and alveoli are airways within the lungs. The series of tubes formed by the branching bronchi are known as respiratory tree. The alveoli are sites of gas exchange between air and blood. Alveolar sac walls are thin and richly vascularized by a dense network of capillaries. Elastic collagen fibers form a tenuous support structure for these capillary sacs. Alveolar cells are extraordinarily thin and allow the free diffusion of gases to all parts of the alveoli and capillaries. In normal resting state, inspiration lasts about 2 seconds and expiration approximately 3 seconds. This rhythm is controlled by inspiratory and expiratory neurons, located in the medulla. Many chemoreceptors monitor oxygen, carbon dioxide and hydrogen ions (pH) concentrations and transmit signals to the respiratory center to regulate the respiratory activity. The central chemoreceptor is located in the medulla and reacts to elevated CO_2 levels in body fluids (hypercapnia). The peripheral chemoreceptors are located in the neural tissue of the carotid body and in the aortic body. These bodies are located in specific points in the arteries of the same name. They react to low O_2 levels in body fluids (hypoxemia). Hypercapnia and hypoxemia will normally increase the rate and depth of breathing.

Analysis of respiratory function relies on the functional capacity of other systems, such as the cardiovascular and the muscular, and may vary with height. Respiratory function can be easily impaired by pathological conditions such as emphysema or by exposure to environmental pollutants, including those associated with smoking (KLOCKE, 1977). Carefully elaborated studies helped finding what seems to be the effects of aging on respiratory function (SHOCK, 1985). There seems to be very few age-related changes on respiratory functions at rest. Significant effects of aging appear, however, when the respiratory system is under stress. Respiratory capacity decreases about 50% at 85 years old. Older people lose their reserve and these changes related to the respiratory function were interpreted as the result of intrinsic changes in the components of the connective tissue of the lungs. Such changes result in decreased elasticity of the alveoli. As a result of these kinetic changes, lungs of older adults are less able to provide enough ventilation and gas exchange to meet O_2 demands from the body at maximum effort levels. Smoking adds chemical damage to these intrinsic age-related changes in the respiratory system.

4.2.6 Digestive system

The main function of the gastrointestinal and digestive system (GDS) is to break down food so that body cells may absorb nutrients and eliminate waste products. The gastrointestinal tract (GI) has also secondary endocrine functions intimately connected with digestive and metabolic processes. The digestive system is a long tube with regional specialization for different functions. Among digestive system components are many highly specialized organs, which may belong both to the alimentary canal as to accessory organs. The normal functions of each of its components are summed up in Table 3. Few age-related changes are perceived in the digestive system, unless the population is assessed to detect occult gastrointestinal diseases and/or deleterious habits, e.g., excessive alcohol consumption. Another complicating factor is the cultural and/or economic aspects that may restrict the types of foods recommended for ageing individuals. This scenario was reviewed and summarized by Whitbourne (1985) and Spence (1988).

At least two general changes affect the digestive tract: the muscle contractions become weaker, resulting in a slowing down of the peristaltic motion of the alimentary canal, and the glandular secretions tend to diminish somewhat. These alterations are the results of more fundamental age-related changes. The decrease in glandular activity leads to specific glandular changes. The mouth becomes drier as the volume of saliva diminishes. Gastric secretion can diminish by as much as 25% by 60 years of age. In the small intestine, atrophy of the mucosal lining mildly reduces the absorption rate. All four layers of the large intestine undergo atrophy, leading to a weakening of the intestinal wall and a concomitant increase in the incidence of diverticulosis. The most significant changes in digestive function related to age concern the relationship between vitamin D and calcium absorption. Ca^{+2} absorption in the intestine decreases after age 70. The process of active transport of Ca^{+2} is regulated by the blood levels of the active form of vitamin D (calcitriol). The decreased absorption of Ca^{+2} might be due to reduced serum levels of active vitamin D. The decreased Ca^{+2} uptake might be due to paradoxically higher blood levels of calcium as a result of bone resorption, which results in a decreased level of active vitamin D formation and a consequent continued low level of calcium absorption. However, this age-related change can be modulated by proper nutrition and exercise.

Table 3. Normal structures and functions of the gastrointestinal tract organs.

Region	Function	Enzymes structures and/or characteristic processes
Alimentary Canal		
Mouth	Mechanical maceration	Teeth
	Wetting action, beginning of carbohydrate digestion	Saliva containing enzymes (salivary amylase)
	Appetite stimulation	Taste buds
Pharynx and esophagus	Swallow	Esophageal peristalsis
	Transport of food to the stomach	
Stomach	Eliminate exogenous bacteria	Hydrochloric acid secreted by gastric glands and also pepsin
	Protein digestion	Muscle contractions
	Conversion of chewed food into semiliquid form	Stimulation and secretion of gastric juice
	Production of gastrointestinal hormone	
Small intestine	Completion of protein and carbohydrate digestion	Several enzymes released by the intestinal wall and pancreas
	Beginning and completion of lipid digestion	Pancreatic enzymes and hepatic bile
	Nutrient absorbed into the blood stream	Intestinal villi
	Production of secretin	Stimulation of bile secretion and pancreatic juice
Large intestine	Absorption of water and minerals	Microvilli on surface of cells lining the intestinal wall
Glands and accessory organs		
Pancreas	Two types of cells:	Pancreatic amylase, lipase
	Acinar cells produce many enzymes	Insulin, glucagon,
	Islet cells produce hormones	
	somatostatin that regulate blood sugar levels	
Liver	Storage and release of carbohydrates; conversion of amino acids into carbohydrates	All processes happen in all cells
	Fat packaging for transport	
	Regulation of cholesterol levels	
	HDL and LDL synthesis	
	Bile secretion	
	Fat-soluble vitamins storage	
	Synthesis of proteins present in blood plasma	
	Inactivation of hormones	
	Inactivation of foreign substances, e.g., alcohol, drugs	

Source: Adapted from Arking (2008).

These aspects were summarized by Whitbourne (1985) and Spence (1988) and here presented (ARKING, 2008).

Recent researches demonstrate how important intestinal microbiota is to human health. Evidence that shows health researchers great interest in the subject is “Nature” magazine volume 489, 2012, publishing five review articles on intestinal microbiota. Lozupone et al. (2012) discuss the diversity, stability and elasticity of gastrointestinal tract microbiome. Dysbiosis or this microbiome disorder can be the cause of metabolic disorders that trigger many diseases (SANDERS, 2011).

4.2.7 Excretory system

The kidney is internally divided in two distinct regions, the outer cortex and the inner medulla. The inner medulla furrowed appearance is due to several more or less parallel tubules and ducts. The renal arteries elaborately divides into branches, originating the afferent arterioles that subdivide forming a capillary network, the glomerulus, enclosed in the Bowman's capsule. The capillary convergence creates efferent arterioles, which then subdivide in a network of capillaries surrounding the tubules before returning to the venous circulation. The nephron is the functional unit of the kidney and is responsible for eliminating chemical waste from the bloodstream and for regulating the concentration of salt and water in the body. Each kidney has millions of these functional units, the nephrons. The kidney filters approximately 12.5 mL of fluid per minute, or 180 L per day, through the glomerulus and into the Bowman's capsule. This filtrate contains digested food, minerals and waste products, but it does not contain blood cells or high-molecular-weight protein molecules. These components are essential for the normal functioning of the body. Approximately 99% of this fluid is reabsorbed in the kidney tubules and the body produces only 1 to 2 L of urine per day. The urine flows through the ureters to the bladder, where it is stored until it is expelled through the urethra. The bladder is a hollow muscular organ that can store approximately 600 mL of fluid. Stretch receptors in the urinary bladder wall initiate muscle contractions that will empty it, usually when the bladder is only half full.

The kidney of aging individuals gradually loses mass, most of which in the cortex as a result of intrarenal vascular changes. These vascular changes take place independent of hypertension, although they are aggravated by that condition. The origin of these changes is not clear. One hypothesis, however, suggests that they are due to a thickening of the visceral layer of the glomerulus. This condition would give rise to a retention of impaired proteins in the blood, resulting in proteinuria (SAMIY, 1983). This proteinuria develops and might cause the glomerular sclerosis and vessels abnormalities. Since the kidney has a very large reserve capacity, age usually has little effect on the body's ability to maintain fluids and electrolytes balances under normal conditions. When under stress, however, older people ability to cope is not as good as that of younger people, and the decreased number of nephrons begins to be evident in longer response times and a general failure to maintain homeostatic equilibrium.

Both cross-sectional (TOBIN, 1981) and longitudinal (SHOCK et al., 1979) studies have demonstrated that creatinine clearance (a measure of kidney function) declines with age and appears to be an intrinsic change. The longitudinal study also showed that there is a great deal of normal variability in this parameter between individuals. Interestingly, individuals who died during the study showed a greater rate of decline in renal function during the 10 years preceding death than did survivors. These results are in agreement with data from the literature, which suggest the existence of individual differences and the heterogeneity of the human population.

4.2.8 Nervous system

The structural complexity of the nervous system and the processes by which brain activity is transduced into mental processes justify the interest of neuroscience researchers in seeking to unlock the secrets of functioning of this organ, which is vital to human beings. Here will be presented a brief and partial summary of the neurological basis for some of the aging effects observed in the central nervous system (CNS) and to allude to some other possible effects in cognitive and intellectual functioning. Each of the different regions of the brain is involved with different aspects of sensory, motor and/or mental activities. The human brain is the most complex living structure known to us; it is probably safe to say that it is the most complex structure in nature. The fifty billion or so neurons in the human brain do not function as isolated units the way the cells of the liver or kidney do. Individual neurons may transmit messages to one, two or a few neurons, or to as many as 1000 or more other neurons. The message is transmitted from one end of a cell to the other terminal as an electrical impulse. The impulse cannot jump the gap, or synapse, between the cells and it must be converted to a chemical signal at the start of the synapse and then converted back to an electrical impulse at the other side of the synapse before continuing through the circuit. Neurotransmitter is the generic term for any of the diverse chemical compounds that regulate intercellular transmission across the synapse (Figure 3).

The gray matter of the brain is composed of the nerve cell bodies, whereas the white matter contains no nerve cell bodies or dendrites and is formed by the myelinated nerve fibers. The gray matter is located on the surface portions of the brain and is known as the cerebral cortex, the cerebellar cortex and so on. Most of the cells of the CNS are neuroglial cells and not neurons. The neuroglial cells are a diverse group of non-nervous cells that assist in supporting and maintaining the neurons, contributing to their functional ability.

During the 20th century, at least a dozen studies were carried out on changes in brain weight or volume as a function of aging. The brain increases in size from about 357 g at birth to a peak size of about 1300 g at age 20 years. This weight is maintained until about 55 years, which marks the beginning of a progressive decline in brain weight through the age of 80 years (DAVISON, 1987). The result can be as much as an 11% decrease in mean brain weight of the brain in older individuals compared to young adults. There is not a solid correlation between

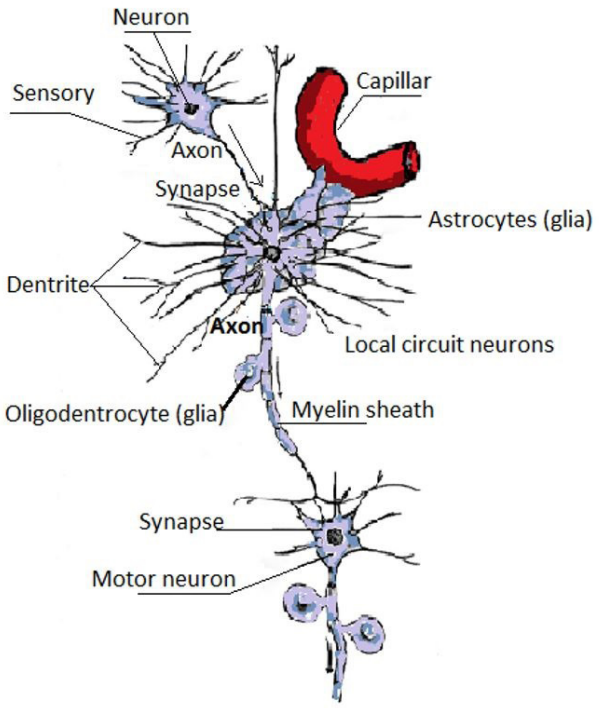

Figure 3. Neural circuit. A large neuron with multiple dendrites receive synaptic contact from a sensory neuron (superior skeleton). The same large neuron sends its myelinated axon into a synaptic connection with a motor neuron at the lower part.

these changes and changes in the affected individuals intellectual capacity (DUARA et al., 1985). The recent use of computed tomography (CT) made longitudinal studies possible, which have added valuable knowledge in the evaluation of the functional importance of such general anatomical changes. Most of the researches on aging over the years have focused on the characterization of neural structure and function, and how common age-related changes affect functional capacity. The general loss of brain weight and size with aging is probably due to the loss of individual neurons, especially associative neurons. Most of the loss occurs after the age of 60 years. On the other hand, dendritic decreases may as well represent functional changes in neural circuits at synaptic level. Other functional changes probably involve the synthesis of neurotransmitters and the brain energy metabolism.

These neural surfaces are shown without the extensive enclosure of glial cells that involve the neural branch that extends until the upper right capillary (BLOOM et al., 1985).

One of the most important functions of the brain is the integration of body activities through neuroendocrine and immune system. Some of the diseases and degenerative diseases affecting older people may have their origin in the disruption of a particular aspect of this system of intercellular communication. The brain cannot function normally without sensory stimuli. All senses undergo age-related changes that alter the perceptions of reality. Therefore, to maintain functional capacity it is important to adopt prosthetics devices (hearing aids, glasses and others) and/or adaptive changes in behavior.

4.2.9 Immune system

The immune system protects the human body against microorganisms and/or toxins and molecules produced by them and molecules (usually proteins) improperly absorbed (antigens), which are perceived as foreign substances to the body. The ability to distinguish between what is foreign and what is not is a fundamental characteristic of the immune system. The bone marrow and the thymus are the main structures of the immune system and they are sources of precursor cells. The spleen and the lymph nodes are secondary structures, where the immune response starts. Figure 4 shows the relationships between these structures.

Immune system cells consist mainly of B and T lymphocytes. Lymphocytes have special subtypes, in which all have receptors in the cell surface and may respond to a restricted type of structurally similar antigens. The antigen is the molecule of stimulus, not of its own, which induces a highly specific immune response. B lymphocytes are responsible for humoral immunity, which is carried out by the production and secretion of molecules of specific antibodies (immunoglobulins) in blood and lymphatic circulation. Immunoglobulin molecules bind to specific antigens such as bacterial toxins, which induced their formation, inactivating them. T lymphocytes are responsible for cell-mediated immune reactions that comprises a set of different responses. One of these responses is to stimulate growth and differentiation of B lymphocytes (hence, regulate humoral response of antibodies). Another response is the production of a subpopulation of T cells ("killer" T-cells) that can directly recognize and destroy strange or not own cells.

The most obvious morphological age-related change of the immune system is the involution or partial atrophy of the thymus, which becomes apparent in sexual maturity. This size reduction is primarily due to the atrophy of the cortex responsible for producing many thymic hormones essential for the maintenance of immune functions. Decreased level of thymic hormones is followed by decreased number of T lymphocytes. The relatively large number of immature T lymphocytes found in the involuted thymus suggests that decreased competent cells means the decreased ability of the thymus to differentiate many immature lymphocytes. It is clear that immune senescence results in a selective decrease of secretory factors and the low level of such factors is what can lead to changes in the composition of immune cell population and in immune function (STERNBERG, 1994), Table 4. At the beginning of this presentation we adopted the definition of natural or biological aging as a series of functional and

structural changes that occur in all people with greater or less intensity during their existence. These changes were conceived as: cumulative, progressive, intrinsic and deleterious (CUPID).

4.2.10 Reproductive system

The reproductive systems of both genders have functional losses with aging. These changes are more pronounced in women, with a gradual loss of fertility from midlife age onwards. The reproductive system is very different from other body systems as concerns control mechanisms of its development, acquisition and loss of function. In utero the primitive gonads are different from other body tissues, because the beginnings of both the ovarian and testis primordium may potentially develop male or female structures. At around the eighth week of pregnancy there are conditions to develop one structure or the other, as the result of the interaction between genetic and hormonal factors. Abnormal sexual development is usually the result of failures in these processes of interaction and control. Birth is followed by a gonadal rest period until later activation by gonadotropins, produced by the pituitary glands. The final maturation of the reproductive system starts with this hormonal activation. This period of growth and maturation is known as adolescence. Puberty marks the end of the maturational state, as soon as reproduction becomes possible, even if it does not occur.

4.2.11 Reproductive aging in women

4.2.11.1 Normal functions

The two ovaries store and release alternatively a mature ovum each month into the uterine tubes for fertilization and transport to the uterus. A woman ovulates perhaps 500 or fewer eggs or less in her lifetime; this is just a tiny fraction of the total cells (oocytes) at birth, and eggs at puberty, as shown in Table 5. This atresia ("wastage") is a normal component of follicle development and probably represents a selection mechanism by which only the fastest growing oocyte is chosen for ovulation. Women with early menopause usually have ovaries devoid of follicule. The functional life of the human ovary appears to be proportional to its follicular store and is not simply a matter of chronological age (WISE, 1986).

The hypothalamus is the primary regulatory organ of the reproductive system. It contains neurons that signal and secrete from their axon endings various protein hormones instead of neurotransmitters. These hormones, usually called gonadotropin releasing hormones, travel via a special blood capillary network to the anterior pituitary, where they stimulate the pituitary cells to secrete the two gonadotropin releasing hormones: the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). FSH stimulates the development of 10 to 20 follicles, bringing

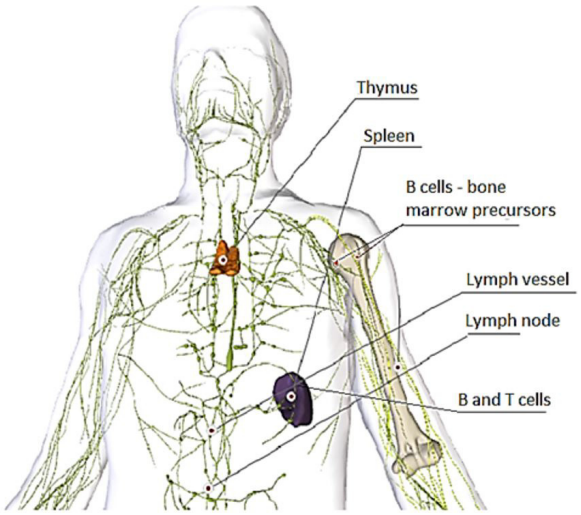

Figure 4. The immune system cell traffic. The terms "T cell" and "B cell" refer to the lymphocytes from the thymus and the bone marrow, respectively. Source: Based on Spence (1988).

Table 4. Immune Senescence.

Secretory factors	Changes of functions
1. Thymus	
Thymosin α-1	→ Decrease in:
Thymulin	Secretory factors
Thymopoietin	
Thymic humoral factor	
2. Stem cell differentiation	→ Decrease in:
Affected by:	Auxiliary T cell ratio
Bone marrow	Alloantigen-specific Tk
Thymosin	Number of natural killer cells
Colony-stimulating factor	Increase in:
Interleukin-3	T cell ratio
	B cell/T cell ratio
	Changes in:
	B cell characteristics
	Antibody production
	→ Increase in:
	Tissue graft tolerance
3. Consequences of 1 and 2	Cancer incidence
	Autoimmune disease
	Infectious disease

Source: Sternberg (1994).

Table 5. Effects of aging on the number of oocytes in women's ovaries.

Age	Estimated number of oocytes
Fetus (4 months)	3,500,000
At birth	733,000
4-10 years	500,000
11-17 years	390,000
18-24 years	162,000
25-31 years	80,000
32-38 years	62,000
39-45 years	11,000

Source: Based on Talbert (1977).

about an elevation in the blood level of estradiol. Only one follicle grows fast enough and is mature to be able to respond to the next signal provided by LH. The level of LH in the blood increase significantly just before ovulation. LH stimulates the rupture of the follicle and the extrusion of the ripe ovum, a process that constitutes ovulation. The mature follicle continues to grow, turning into a corpus luteum, which produces two other hormones, the level of gonadotropin releasing pituitary hormones rises and a new hormonal and ovulation cycle begins.

4.2.12 Age-related changes

The cessation of the menstrual cycle is the major age-related change to women. Follicular deficiency is the most striking feature of the human ovary after menopause. Clearly, the depletion of follicles results in decreased levels of ovarian estradiol secretion, which in turn can be responsible for high levels of FSH and LH observed in middle-aged women before menopause. The consequences of decreased ovarian estradiol are widespread, because many other tissues depend on this hormone for their normal maintenance. The tissues affected by estradiol decline include not only components of the reproductive system itself and components of secondary sexual characteristics, but also non-reproductive organs, e.g., skin, skeleton and cardiovascular system. Changes in tissues probably arise due to this action of LH and FSH hormones on the ovaries, which is blocked by prolactin, a hormone usually produced at high levels only when a woman is breast feeding. This inhibition underlies contraceptive effects of breast feeding.

As the levels of the two ovarian hormones, estradiol and progesterone, increase, they act on the hypothalamus to inhibit the production of the gonadotropin releasing hormones. The decrease in these hormones results in a lower production of LH and FSH by the pituitary. If fertilization has occurred, implantation of the fertilized egg in the endometrium (the tissue that internally covers the uterus) stimulates the production of progesterone independent of the hypothalamic-pituitary control axis, maintaining the pregnant state. Progesterone production stops in the absence of fertilization and implantation. Without hormonal support, the endometrium cannot sustain itself and a large portion of it is sloughed in the menstrual blood flow. As a result of the low level of ovarian hormones and many gene activities induced by hormones. Heat flashes are associated with a pulsatile release of LH and they can be effectively eliminated by estrogen therapy.

4.2.13 Reproductive aging in men

4.2.13.1 Normal functions

The sperm (male reproductive cell) is produced in the testis. Each testis is subdivided into approximately 250 compartments, and each of these compartments is condensed in highly coiled seminiferous tubules. The sperm are produced continuously inside the tubules. The sperm is a specialized and highly differentiated cell, with the task of delivering one inactivated haploid set of chromosomes to the ovum. While they are in the testes, the sperm remain inactivated, they become partly motile only after they spent around 18h in the epididymis. They become fully motile and mature only in the female reproductive tract. The seminal fluid consists of the secretions of the seminal vesicle, the prostate and the bulbourethral glands. A normal man can release, in each ejaculation, about 300 to 400 million sperm, although only one can fertilize the ovum. The remaining sperm cells must play an important accessory role, since men with less than 20 million sperm per milliliter of semen are usually sterile.

The male reproductive system is under a less obvious form of neuroendocrine control than the female reproductive system. Besides producing sperm, the testes secrete testosterone, the male sex hormone. This hormone is responsible for the normal functioning of reproductive accessory glands and for development and maintenance of secondary sexual characteristics. Testosterone is produced by the Leydig cells in the testis. These cells are activated by LH and the effect is intensified if FSH is also available. The maintenance of seminiferous tubules structure and the development of the sperm in the tubules depend on the combined effects of FSH and testosterone. Therefore, the same control of the hypothalamic-pituitary-gonodal axis is activated in both genders.

4.2.14 Age-related changes

Testosterone levels decrease with age. Even more significant are the alterations in circadian rhythm that is characteristic of testosterone production in older men. The decrease in testosterone level is accompanied by an increase in LH levels and by a loss of the pulsatile LH secretion that is characteristic of young men (BREMNER et al., 1983). Maybe because an insufficient amount of LH is produced, or because the Leydig cells cannot respond to LH increase, testosterone levels in the blood do not increase. This situation is analogous to that of women after menopause (WHITBOURNE, 1985).

A non-pathological change that occurs frequently in male senescence is prostatic hyperplasia, which represents a benign growth of the organ, often compressing the bladder and squeezing the urinary tract, causing discomfort and reduced capacity of retaining urine.

Pharmacological management can be done with “combodart®”, indicated for the treatment of benign prostatic hyperplasia (BPH) in men with enlarged prostate and to prevent the following symptoms: increased volume of the prostate; improve urine flow and reduce the risk of its complete blockage; reduce the risk of BPH surgery. BPH is caused by the excessive action of DHT (dihydrotestosterone).

Combodart is the combination of two active ingredients: 1) dutasteride, which reduces the amount of DHT produced by the body, resulting in the reduction of the prostate size and hence in the relief of symptoms; 2) tamsulosin relaxes the prostate gland muscles and help with the passage of urine and improvement of the symptoms.

Decreased fertility related to aging seems to be associated more with cultural than with physiological events. Testosterone levels decline may be associated with decline in Leydig cells, which in turn may be associated with decline in sexual intercourses.

5 Healthy aging and longevity

Holliday (1996a, b) categorically stated that "the study of gerontology must have a central position in biomedical research" if we take into consideration the considerable growth in most countries older population and if we hold a realistic hope for lowering the ever increasing public health costs without adversely affecting health care quality and longevity. The prospect of a natural and healthy aging demands from each individual the awareness that life runs out and time remains immutable, but during life operate intrinsic factors that are harmful and will corrode with greater or lesser intensity and speed the human body, leading to diseases and premature death. It is everyone's duty to intelligently struggle with every way possible the deleterious effects on health in order to delay them and have a healthier and longer existence.

According to Garry (2001) genetic research has rapidly advanced. One of its goals is to determine the effects of genetics in chronic disease development. Genetic epidemiology relates genetic traits that can be affected by environmental factors and family distribution of diseases and their distribution in different human populations. The development of new procedures for detection of genetic polymorphism helped professionals to more precise and specifically identify the risk of disease in patients. In the future, presymptomatic testing may replace family history to determine the risks of an individual in what concerns the most important chronic diseases. Coronary heart diseases, dementia and diabetes are chronic aging-associated diseases, prevalent in older populations and are significant causes of functional ability loss. Each of these disorders is identified with or is suspected of relying on genetic and environmental risk factors. For example, independent studies conducted among different racial groups found that the frequency of the APOE4 allele of apolipoprotein E is higher in patients with Alzheimer's disease than in controls with the same age (CORDER et al., 1993). The APOE-4 allele is also associated with increased LDL cholesterol, which increases the risk of coronary heart disease (LENZEN et al., 1986). More recently (FEDER et al., 1996) discovered the gene (HFE) responsible for the heritability of hemochromatosis. This gene has been used to identify presymptomatic homozygous individuals for the faulty gene. This finding allowed that phlebotomy (bloodletting) started before the iron storage reached dangerous levels.

In the past decade, the availability of genomic technology represents a great advancement for genetics of obesity study (MORENO-ALIAGA et al., 2001). Human genetic differences can be detected at the allele-specific polymorphism level (haplotypes). The combination of multiple genes can range from polygenic (many genes with relatively low contribution) to oligogenic (few genes with high contribution and measurable effects, usually expressed on a residual polygenic background (MARTI; MARTÍNEZ, 2006). According to Marti et al. (2008), more than 127 genes have been appointed as candidates to participate in the development of obesity in human beings. There is evidence of the participation of 22 genes in at least 5 different populations. An increasing number of studies on the influence of gene-environment interactions on obesity using the epidemiological, observational or intervention studies approach. Positive evidence have been found for the following genes associated with adiposity: lipid metabolism or energy regulation such as PPARγ^2 (Pro12Ala), β-adrenoceptor2 (Gln27Glu) or uncoupling proteins 1, 2 and 3. Variants of genes associated with the regulation of appetite such as melanocortin and leptin receptors has also been studied.

The diagram in Figure 5 illustrates recent findings related to epigenetic factors and bioinformatic methods such as a tool for elucidation of genotypes in different phenotypes.

In the past few decades, food science and health researchers have usually focused on this subject, discovering and proving the existence of several factors both intrinsic and extrinsic, which pursued with discernment and intelligence, can lead us to a healthier life. In a general and simplified way, we can imagine this factors grouped in three major classes, including (Figure 5): 1) environmental factors (alimentation, environment, lifestyle); 2) epigenetic factors that will act directly or indirectly on the genetic codes, producing modified phenotypes; 3) lastly, the original genetic codes, which may or may not be modified (epigenetically) to produce the total set of proteins involved in the general metabolism, for the benefit of the individual.

What may be inferred by the careful analysis of Figure 5 is that the number of messenger RNAs (m-RNA) translated into synthesized proteins is much greater than the number of genes established for the human species (maximum of 30,000 genes) by the human genome project. This divergence led scientists from various countries to seek an explanation to this fact and from where a new discipline was created (Epigenetics), which started to study the phenomena of transcription and translation (Figure 5) responsible for a large number of proteins (> 500,000)

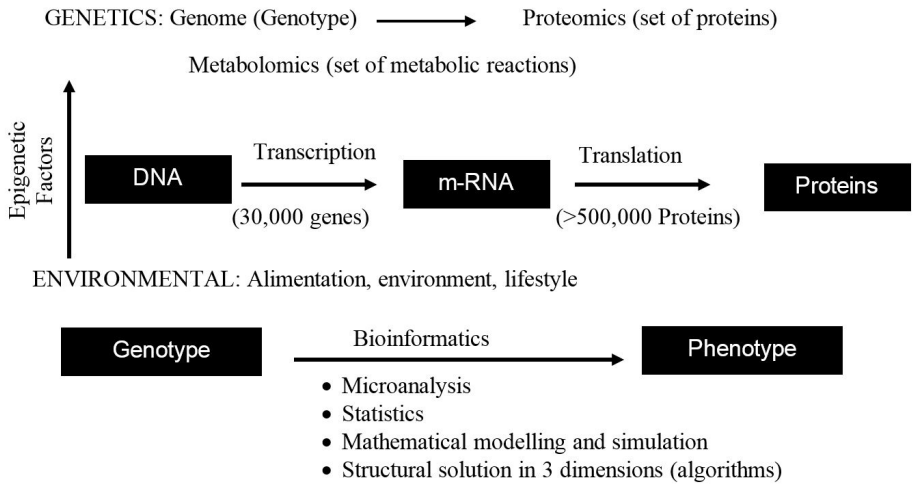

Figure 5. Determinants of health: quality of life, longevity.

involved in the human metabolism. Bioinformatics was then the field of science capable of explaining the transformation of genotypic characters into phenotypic characteristics. One can infer from the foregoing that what we are and our quality of life depend on original genetic characters that we inherit from our parents and ancestors, and how this inheritance may have been modified (epigenetically) by environmental factors, in a simplified way, in Figure 5 as alimentation, environment and lifestyle.

The Research Center on Human Genome and Stem-Cells (CEGH-CEL) of the University of São Paulo (USP) on health well being and aging (Sabe) initiated in 1999 in the Public Health School a survey of a large sample of elderly, including DNA analysis of about 130 (80+years) all in good health. In total the USP researchers sequenced the axome (part of their genome codifying proteins of more than 1.300 residents in the city of São Paulo with 60 or more years of age. The first results of 609 participants, were published in March this year in Human Mutation (NASLAVSKY et al., 2017). There were found 207 thousand genetic variants which had not been described in the international molecular data bank.

Brazilians are highly admixed with ancestry from Europe, Africa, America, and Asia and yet still underrepresented in genomic databanks. The above cited paper present a collection of exomic variants from 609 elderly Brazilians in a sensusbased cohort (SABE609) with comprehensive phenotyping variants which were deposited in ABraOM (Online Archive of Brazilian Mutations), a Web-Based public database. Population representative phenotype and genotype repositories are essential for variant interpretation through allele frequency filtering; since elderly individual are less likely to harbor pathogenic mutations for early – and adult-onset diseases, such variant data bases are of great interest. Among the over 2.3 million variants from the present cohort 1,282,008 were high-confidence calls. Importantly, 207,621 variants were absent from mayor public data bases. It was found 9,791 potential los-of-function variants with about 300 mutations per individual. Pathogenic variants on clinical relevant genes (ACMG) were observed in 1.15% of the individuals and were correlated with clinical phenotype. These observations illustrate the relevance of collecting demographic data from diverse, poorly characterized populations. According to the authors of this paper, Census-based datasets of aged individuals with comprehensive phenotyping are invaluable resource toward the improved understanding of variant pathogenicity. A few recent publications which supported the above mentioned investigation is cited below (CHEN et al., 2016; DEWEY et al., 2015; FERNANDES et al., 2016; HENN et al., 2015; LEK et al., 2016).

Today there is evidence that most genes causing obesity does not have a primary etiological role, but probably act as modifiers agents of environmental factors such as diet and physical activity. These findings infer that factors related to lifestyle should be investigated in genetic studies and that genetic factors should be determined in dietary interventions and in clinical trials. Therefore, it is crucial to take into account environmental and genetic factors when programs are designed for the prevention and treatment of obesity (MARTI et al., 2008).

The molecular mechanisms of aging are the subject of much research and it has helped potential interventions to delay aging and degenerative diseases accompanying aging. The aging process is frequently affected by environmental factors, and calorie restriction (CR) is by far the most effective and established environmental manipulation to increase longevity in various animal models. However, the precise mechanisms by which calorie restriction affects life span are still not clear. Epigenetic mechanisms have recently been recognized as major contributors to nutrition-related longevity and aging control. Two primary epigenetic codes,

DNA methylation and histone modification, are believed to dynamically influence chromatin structure, resulting in expression changes of relevant genes (LI et al., 2011). In most studies on calorie restriction the limitation of total calories derived from carbohydrates, fats, and proteins was to a level 25%-60% below that of control group fed ad libitum, however containing all essential nutrients, extension in life span can approach 50% in rodents (KOUBOVA; GUARENTE, 2003; WEINDRUCH et al., 1986; KETONEN et al., 2010; WU et al., 2008; SUN et al., 2004).

Calorie restriction affects epigenetic processes via two primary mechanisms: DNA methylation and histone modifications. Regulation of DNA methylation during calorie restriction involves the activation of DNA methyltransferases (DNMTs), resulting in silencing of expression of target genes such as $P16^{INK-4\alpha}$ and Ras, due to the hypermethylation of these genes. Histone remodeling induced by calorie restriction includes primarily methylation and histone acetylation. Effects of deacetylation due to the activation of histone deacetylase (HDAC), like sirtuin 1 (SIRT1) deserves special attention because it has a fundamental role in the regulation of aging and extension in life span associated with calorie restriction (LEIBIGER; BERGGREN, 2006; COHEN et al., 2004). Uncommon, SIRT1 enzyme activity is very dependent on the NAD/NADH ratio, a key indicator of O_2 consumption and metabolic rate of the respiratory chain; it suggests that this protein is strongly associated with the metabolic state of cells. SIRT1 activation often occurs in different organs affected by calorie restriction, whereas SIRT1 inactivation can hinder the extension in life span, denoting its central role in regulating the extension in life span by calorie restriction. Effects of deacetylation due to the activation of SIRT1 and histone deacetylase 1 (HDAC1) by calorie restriction lead to changes in the expression of key genes such as p53, Foxo, Ku70, and $P16^{INK-4\alpha}$ that hence have negative gene expression, and hTERT and PGC-1αwith regulation(+), meaning increased expression. As a result, the epigenetic regulation actively reverts aberrant gene expression during calorie restriction, which contributes to the delay of aging and extension in life span. Caloric restriction (CR) protects against many cerebral pathological conditions that are associated with excitotoxic damage and calcium overload, although the mechanisms are still poorly understood. CR increases electron transport chain activity, enhances antioxidant defenses, and favours mitochondrial calcium retention capacity, in the brain (AMIGO et al., 2017). These changes are accompanied by a decrease in cyclophilin D activity and acetylation and an increase in SIRT3 expression. This suggests that SIRT3 mediated deacetylation and inhibition of cyclophilin D in CR promote the inhibition of mitochondrial permeabilits transition, resulting in enhanced mitochondrial calcium retention. The results that enhanced mitochondrial calcium retention capacity underlies the beneficial effects of CR against excitotoxic conditions. This protection may explain the many benefitial effects of CR in the aging brains.

Another interesting recently published paper (LUÉVANO-MARTÍNEZ et al., 2017) found that mitochondria from *ad libitum* animals presented an increased content of lipoperoxidases and of cardiolipin. Cardiolipin plays a key role in mitochondrial function, signaling and stress response. Mitochondrial levels of the enzymes involved in cardiolipin biosynthesis and remodeling were found to be hyperegulated in CR animals. When the mitochondria membranes were fractionated the outer membrane presented the higher content of cardiolipin, indicating that CR promotes extensive mitochondrial remodeling, decreasing oxidatively damaged lipids. This changes in membrane properties are consistent with and maybe causative of changes in mitochondrial morphology, function and turnover, previously found to occur in CR. Figure 6 summarizes the most important metabolic events as a result of calorie restriction.

The readily reversible character of epigenetic changes offers a great potential for their use in specific interventions to revert epigenetic changes during aging, which may have a significant impact on the retardation of aging and on reducing the risk of age-related diseases. Although knowledge of the role of epigenetic mechanisms in calorie restriction and their health-related impacts is relatively limited by the end of this century, new studies will certainly bring more precise interpretations of these complex interactions, helping to find new dietary or pharmacological interventions that promote human longevity. The profound effects of SIRT1, which somehow reproduce resveratrol effects in its influence on the aging processes, is a promising example that new improvements in the quality of life, especially of older citizens, might take place in the near future.

As stated in the leading edge review (LÓPEZ-OTIN et al., 2013) the nine hallmarks of aging were divided by the authors in three categories: 1. Primary hallmarks, which causes demage (genomic instability, tellomere attrition, epigenetic alterations, and loss of prosteostasis; 2. Antagonistic hallmarks, which represent responses to demage (deregulated nutrient sensing, mitochondrial disfunction, and cellular senescence); 3. Integrative hallmarks, culprit of the phenotype (stem cells exhaustions, altered intracell communication). The authors go on to suggest possible future interventions aiming at extending human healthspan, such as: 1. elimination of damaged cells; 2. telomerase reactivation; 3. epigenetic drugs; 4. activation of chaperons and proteolytic systems; 5. dietary restriction: ilsulin-insulin growth factor and m-TOR inhibition, AMPK and SIRTs activation; 6. mitohormetics and mitophagy; 7. clearance of senescent cells; 8. stem cells-based therapies; 9. anti-inflammatory drugs, and blood-borne rejuvenation factors.

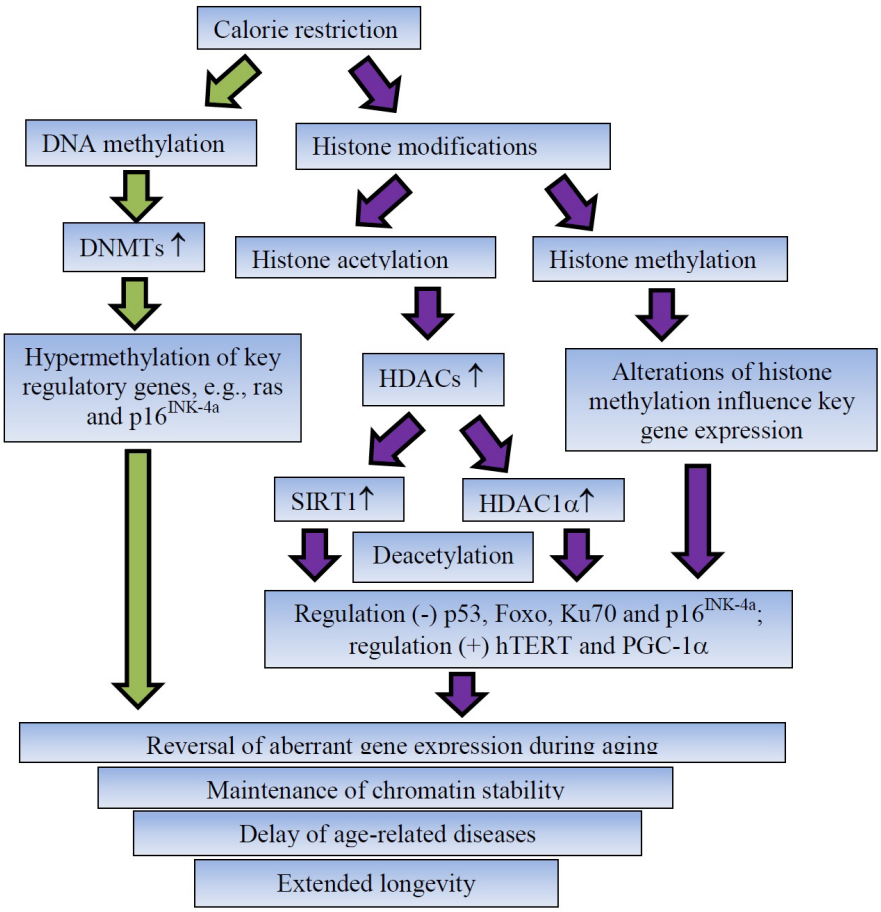

Figure 6. Epigenetic pathways regulated by calorie restriction. Source: Adapted from Li et al. (2011).

Moreover, according to Patras and Tudose (2013) it is important to consider in the study of interactions between genotype and food consumption and its effects on health the following complicating factors: 1) diversity in the genetic makeup of human beings; 2) the complexity of chemical compounds naturally found in food and how food is prepared for consumption; 3) the numerous changes that the human metabolism can undergo to cause diseases. For example, almost 300 genes have been associated with obesity and at least 150 genetic variants seem to be responsible for type 2 diabetes. Besides the biological complexity, the nutritional science research has certain methodological limitations, including those related to food frequency questionnaires.

6 Importance of nutrition and life style in the aging process and life span

6.1 Nutrition

Aging is conceptually a continuous and irreversible process that begins in the mother's womb, as a fetus and an embryo. It goes on through all stages of life culminating in physical death. A healthy biological aging depends on a complex scheme of reactions and physiological and biochemical processes comprising: 1) hereditary traits, including genetic adaptations and modifications; 2) influence of environmental factors, the most important of them are the individual's nutrition and lifestyle. Recent researches showed that during the last century the women's average life span increased to 81 years, whereas both genders' life span increased approximately 50%, from 50 to 75 years (SMITH, 1993).

The significant increase in life span is mostly related to the advances in medicine, pharmacology and alimentation, including researches in nutrition and food technology.

Nutrition improved with the development of the functional food concept, through bioactive principles, including new physiological and biochemical properties for nutrients such as proteins and peptides, fats and fatty acids, carbohydrates and dietary fibers, vitamins and some essential amino acids. Bioactive properties were also discovered in phytochemicals components widely distributed in plant foods, as shown in Table 6 (SCHREINER, 2005).

It is not the aim of this review the details about results of numerous papers published on food bioactive

components, which may have beneficial effects on health and also expected to affect somehow and slow aging. Some works are cited here only to show the evolution on this field (RITZ, 2000; ZIMMERMAN et al., 2003; MASORO, 2005; LUCERI et al., 2017; KANEAI et al., 2016; SOUTIF-VEILLON et al., 2016; LIM et al., 2016).

Despite recent findings that specific nutrients and non-nutrients bioactivity of food somehow helps improving health and quality of life and potentially slowing aging, current knowledge about changes on the general metabolism does not completely enlighten the numerous actions and interactions in the human body responsible and indispensable to the processes of natural senescence.

As long as new knowledge on our diet does not allow a deep understanding on their interactions, it is worth turning our attention to well-known diet plans for their practical results, e.g., the Mediterranean diet (MD), profile.

"The mediterranean diet – health and Science", written by Hoffman and Gerber (2012) have updated information on main features of the MD. A comprehensive definition of MD is: 1) Consumption of a variety of fruits, vegetables, seeds, whole grains, herbs, spices and nuts; 2) consumption of fruits and vegetables is higher in Mediterranean countries; 3) leafy green vegetables comprise not only many cruciferous for salads, widely consumed in Northern Europe, but also wild branches and leaves; 4) alliacea, species from the onion and garlic family is consumed in large quantities; 5) seasonal fruits are consumed fresh. Citrus fruits are an important source of vitamin C, figs and dates are important sources of fiber and some fruits are particularly rich in certain phytochemicals, e.g., beta-carotene found in apricot, punicalagin found in pomegranate, monoterpenes found in citrus. Black olives have lower levels of the bitter substance oleuropein than green olives, and for this reason they are processed. Processing methods can have a huge effect on levels of bioactive compounds; 6) legume seeds have a very important role in the MD, especially in lower-income classes. Mashed fava bean seeds is a national dish of Egypt and chickpea is particularly popular in Turkey and in Spain. Legumes are good sources of fiber, phytosterols and lignans; 7) whole-wheat grain products are consumed daily as part of the traditional MD; 8) herbs and spices also define the Mediterranean cuisine and are commonly consumed in quantities much greater than in the Northern European cuisine; 9) nuts and seeds are used in candies and snacks, and they are rich in proteins, fats (predominantly unsaturated), fiber, vitamins, minerals and phytochemicals. Some nuts are particularly rich in certain nutrients, e.g., walnuts contain α-linolenic acid; pistachios contain β-sitosterol; and almonds contain α-tocopherol. The MD is also characterized by high fish and olive oil consumption, reduced consumption of meat and dairy products, promoting a high consumption of monounsaturated fats instead of saturated fats. The basis of food consumption of plant and animal origin in the MD is represented in Table 7.

The Mediterranean diet has become popular for its functional properties and alleged benefits to human health. It is adopted and practiced in all Mediterranean countries and today it is imitated by many countries around the world. Among the most studied and known health benefits we may cite: 1) promoting longevity, (TRICHOPOULOU; VASILOPOULOU, 2000); 2) combat the causes and reduce the effects of metabolic syndrome (BABIO et al., 2009; FERNANDEZ, 2011; STOCK, 2011; GROSSO et al., 2014); 3) improving cognitive function in older people (FÉART et al., 2010); 4) provide appropriate fetal development and size in children at birth (TIMMERMANS et al., 2012); 5) preserving the mineral composition and bone density in menopausal women, contributing to prevent osteoporosis or slow its progress (RIVAS et al., 2013); 6) contributing to prevent metabolic diseases such as chronic inflammation, visceral obesity, type 2 diabetes and metabolic syndrome (GIUGLIANO; ESPOSITO, 2008); 7) indications to combat non-alcoholic fatty liver diseases (VELASCO at al., 2014); 8) contributing to lower overall mortality, incidence of diabetes and the occurrence of cardiovascular events (DOMÍNGUEZ et al., 2013); 9) potential health benefits of the MD, statements of specialists from different countries (TRICHOPOULOU et al., 2014).

Table 6. Functions or actions of some phytochemicals in disease prevention.

Phytochemical	A	B	C	D	E	F	G	H	I
Carotenoids	➢		➢		➢				
Phytosterols	➢	➢						➢	
Saponins	➢	➢			➢			➢	
Glucosinolates	➢	➢						➢	
Polyphenols	➢	➢	➢		➢	➢	➢		➢
Sulfides	➢	➢	➢		➢	➢	➢	➢	
Monoterpenes	➢	➢							
Phytoestrogens	➢		➢						

A: anticarcinogenic activity; B: antimicrobial; C: antioxidative; D: antithrombotic; E: immunomodulatory; F: anti-inflammatory; G: hypotensive; H: hypocholesterolemic; I: control of blood sugar. Source: Adapted from Schreiner (2005).

Table 7. Mediterranean diet: practices for a healthy life (inverted pyramid representation).

Distribution: base/upper levels	Frequency
1- Habits and lifestyle: physical activity, healthy diet (preferably followed by siesta after a meal)	Daily activities that constitute a healthy lifestyle
2- Fruits and vegetables; mainly whole grains and whole grain breads; olive oil; beans, nuts, legume seeds, potatoes; herbs, spices; wine (during meals) and water	These foods constitute the basis of Mediterranean diet and are present in almost every meal
3- Fishes and sea products	Daily or weekly consumption
4- Poultry and eggs, cheese and yogurt	Every 2 days or weekly
5- Meat and sweets	Less frequent (moderate portions)

Source: Oldways (2009).

The abovementioned works are a small sample of the potential health benefits of adopting a Mediterranean diet. The literature on the subject is vast. An important work that must be mentioned is the book edited by Stanner et al. (2013), "Healthy ageing – The role of nutrition and lifestyle". It is a complete research of the task force created by the British Nutrition Foundation and led by professor John C. Matheus.

6.2 Lifestyle

At this point the readers may have noticed that habits and lifestyle are given much importance in the base of the MD food pyramid, e.g., daily physical activity, healthy eating preferably in the company of others, siesta after the midday meal.

In "The longevity bible", Small and Vorgan (2008) suggests eight essential steps to keep an open mind and the body young, namely: 1) prepare your brain for longevity and your body will also be prepared. Mentally stimulating leisure activities such as reading, crossword puzzles or games reduce the risk of Alzheimer's disease by up to 30%; 2) keeping a positive attitude help us to stay healthy and live longer. Optimists have less physical and emotional difficulties, feel less pain, have more energy and are less stressed; 3) it is very important to keep good family and social relationships; 4) always try to reduce the level of stress. Stress is one of the main causes of age-related diseases. The quality of longevity depends on our ability to adjust to environmental influences such as the traffic, the cigarettes, the noise, the smoke, and even the information overload; 5) customize and organize your more immediate space. It is very easy to keep a positive attitude when we have a good health and the best way to ensure this is to adopt a healthy diet and cultivate physical fitness; 6) a program to maintain and achieve physical fitness and longevity should include cardiovascular conditioning, physical and mental balance training, flexibility and muscle strengthening. These are three vital areas of conditioning to maximize health, boost energy levels and prevent many age-related diseases. Regular physical activity can add two or more years to life expectancy and it is needless to say that one should avoid excessive food intake (excess calories), saturated fats, fried food, excessive alcohol intake, and soft drinks, particularly those containing sugar; 8) along with the abovementioned recommendations one should make throughout life medical examinations and functional tests in specialized centers relying on the appropriate professionals.

7 Final considerations

As stated at the beginning of this review, aging or natural senescence can be defined as a series of functional and structural changes that are cumulative, progressive, intrinsic and deleterious (CUPID).

It is known today that these changes may begin in the mother's womb and end with the individual's physical death. These changes may have a genetic, metabolic, or environmental origin, and usually are a combination, throughout life, of all these causes. The most common genetic changes are DNA damage and repair failure, in the mitochondria inclusively, and epigenetic changes. Metabolic factors in the presence or absence of antioxidants (oxidative/reductive imbalance), which leads to oxidative stress and may result in degradation of cellular and metabolic components that are important for healthy survival of the body cells.

We may conclude from this presentation that: 1) The aging process is not genetically programmed. Everything points to the result of cellular and macromolecular damage accumulation, especially of DNA inside cells; 2) External factors can strengthen cell damage. Many types of stress and nutritional deficiencies can accelerate the aging process. Factors such as obesity and smoking are associated with a reduction in telomere length (end of a DNA), a potential biological marker of the aging process; 3) Until now there is a limited understanding of the molecular mechanisms by which nutrients or other constituents of food may affect the cellular and molecular damage responsible for biological aging. The antioxidant components of food seem to offer protection against the abovementioned damages, with evidence that Selenium (Se) can stimulate DNA repair processes.

8 Recommendations for future research

1) Encourage research to develop reliable biomarkers of the human aging process, which might be applied both in observational and in intervention studies, with the aim of reducing the pace of biological ageing; 2) Future studies should examine in detail nutrition positive impact on the maintenance and repair mechanisms of cells in the human body. So as to reach the necessary level of understanding in this field of research, it will be important to take a nutritional genomic approach as Figures 5 and 6 suggest. As mentioned back in this article as part of concept in human aging, nine hallmarks of aging were given. These metabolic hallmarks were fully describe in a very excellent review paper (LÓPEZ-OTIN et al., 2013). We also found it interesting to bring into the present article the line of research and/or interventions suggested by the authors to retard or partially reverse these processes into a helthy aging.

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