



Ageing: Physiological Aspects

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Introduction

The word "Ageing" does not give a good feeling to most of us because of problems and diseases associated with ageing. History of the world is replete with tales of individuals trying to stave off aging and death. King David wooed young virgins in search of youthfulness. Wealthy people go to private European medical centers for lamb cell injections. Many individuals take megadoses of vitamin E, drink Kombucha tea etc., all in the hope of finding the "fountain of youth". According to social, behavioural, physiological, morphological, cellular and molecular changes, ageing can be considered in many different ways. Ageing, in its broadest sense is the continuous and irreversible decline in the efficiency of various physiological processes once the reproductive phase of life is over (1).

In recent years ageing has become the social and political agenda. Ageing stories, particularly anti-ageing therapies, are a big attraction in newspapers and magazines (2). It has attracted high level of attention from the United Nations, who is focusing its research agenda on ageing for the 21st century (3). Although etiology of aging is important to understand, but it is equally important to differentiate the normal physiological changes from those associated with diseases. The clinician's inability to recognize these differences may result in unnecessary testing, misdiagnoses and mismanagement of the elderly person. An individual may experience these changes differently i.e. for some, the level of decline may be rapid and dramatic; for others, the changes are much less significant. The research field that emerged from the analysis of the process of ageing in an integrated fashion is known as gerontology. The various physiological changes which occur as we age are:

Changes in the cardio-vascular system: There is normal atrophy of the heart muscle, especially in the left ventricle, calcification of the heart valves, loss of elasticity in artery

walls (arteriosclerosis) and intra-artery deposits (atherosclerosis). There is decreased cardiac output, baroreceptor sensitivity and SA node automaticity. The reduced blood flow results in reduced stamina, reduced renal and hepatic function and less cellular nourishment. There is impaired blood pressure response to standing, volume depletion and heart blocks (4).

Changes in the respiratory system: The airways and lung tissue become less elastic with reduced cilia activity. There is decreased oxygen uptake and exchange. The muscles of the rib cage atrophy, reducing the ability to breathe deeply, cough and expel carbon dioxide. There is ventilation/perfusion mismatch and decreased PO_2 . This leads to decreased stamina with shortness of breath and fatigue (5).

Changes in musculo-skeletal system: There is generalized atrophy of all muscles accompanied by a replacement of some muscle tissue by fat deposits. This results in some loss of muscle tone and strength. Some specific implications of this are reduced ability to breathe deeply and reduced gastro-intestinal activity which can lead to constipation or bladder incontinence, particularly in women. Calcium is lost and bones become less dense. This can result in osteoporosis and a reduction of weight bearing capacity, leading to the possibility of spontaneous fracture. Thinning of the vertebrae also results in a reduction in height. In addition, the vertebrae can calcify, resulting in postural changes. The joints also undergo changes. In fact, arthritis, the degenerative inflammation of the joints, is the most common chronic condition in the elderly (6,7).

Changes in skin: The skin loses underlying fat layers and oil glands, causing wrinkles and reduced elasticity. There is increased susceptibility to cold, bruising and bedsores. In addition, the skin develops "age spots" due to deposits of melanin pigment. The hair gradually loses its pigmentation and turns gray. The nails become thicker

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due to reduced blood flow to the connective tissues. The skin becomes somewhat less sensitive to sensations including heat, cold and injury (8).

Changes in the gastrointestinal system: There is reduction in the production of hydrochloric acid, digestive enzymes and saliva. These changes may result in gastrointestinal distress, impaired swallowing and delayed emptying of the stomach. The breakdown and absorption of foods may also be impaired, sometimes resulting in deficiencies of vitamin B, C, and K or in extreme cases, malnutrition (9).

Changes in the metabolic system: The metabolic system is responsible for changing food into energy. After age 25, everyone experiences approximately a 1% decrease per year in their metabolic rate. This overall slowing results in food being less well absorbed and utilized. There is a decrease in the overall metabolism of drugs (10).

Changes in sexuality: Sexual desire and performance may continue well into an individual's eighth and ninth decade although frequency may diminish. Physiological changes in women include atrophy of the ovarian, vaginal and uterine tissues with decreased production of vaginal fluids. In men, sperm production is decreased and prostate enlarges. Both older men and women generally require more stimulation to become aroused and more time to reach orgasm (11).

Sensory changes with aging: Our special senses play a central role in our ability to gather information and to participate in social interactions. These changes are:

i. Changes in vision: In the fourth decade, the pupil begins to decrease in size and there is decreased response to light. Because of these changes, older people require three times the amount of illumination to see as compared to a younger person. Focusing takes longer with an increase in nearsightedness, making small print harder to read. There is loss of accommodation which makes reading and close work difficult. This condition, which is known as presbyopia, can be corrected by wearing glasses with convex lenses. There is thickening and yellowing of the lens of the eye. This results in light diffraction, increased sensitivity to glare, decreased depth perception and more difficulty distinguishing pastel colors, especially blues and greens (12,13).

ii. Changes in hearing: There is a decrease in sensitivity to high frequency tones and decreased discrimination of similar pitches because of changes in the bones and cochlear hair cells of the inner ear. Approximately 30% of all elderly persons have some hearing impairment. It

is an invisible disability which is often covered up or denied by a person who may then be mislabeled as senile, dumb or uncooperative (12,14).

iii. Changes in taste and smell: Taste and smell are interrelated and important for eating as well as checking for hazards in the environment such as spoiled food, smoke and fumes. Older adults experience some decline in the ability to taste resulting from a reduction in the total number of taste buds, especially after the age of 80. Some individuals also experience a decline in their sense of smell, but this is usually because of abnormal conditions such as blockage or disease of the olfactory receptors in the upper sinus (15).

Cognitive changes associated with aging: After age 25, everyone loses nerve cells. Gradually over time, this results in a reduced efficiency of nerve transmission which affect response time and coordination. These changes may also affect sleeping patterns by decreasing the length of total sleep time and REM sleep (16). In spite of these anatomical and physiological changes in brain, studies have found evidence of limited impairment of actual intellectual functioning associated with the aging process. Intellectual ability is one the factors affecting functioning in later life. The various changes in cognition are:

i. Effect on intelligence: Intelligence generally is associated with a range of abilities that allow us to make sense of our experiences: the ability to comprehend new information, the ability to think abstractly, the ability to make rational decisions, spatial ability, numerical ability, verbal fluency, etc. Some abilities (e.g., the ability to think abstractly) are biologically determined and are known as "fluid intelligence." Other intellectual abilities (e.g., verbal fluency) reflect the knowledge and skills a person has gained through life experience and known as "crystallized intelligence." Intelligence tests have demonstrated a pattern of age-related changes in intellectual functioning. These tests show somewhat poorer performance by older people on tests of fluid intelligence, but little or no difference on tests of crystallized intelligence (17).

The fact that older persons perform more poorly on tests of fluid intelligence is due in part to reduced efficiency of nerve transmission in the brain, resulting in slower information processing and greater loss of information during transmission. Other factors affecting cognitive performance are only indirectly related to the aging



process itself. For example, older persons typically have fewer years of education (18).

ii. Effect on learning and memory: Most persons experience a modest increase in memory problems as they get older, particularly with regard to the ability to remember relatively recent experiences. There is impairment of the ability to accumulate new information and to retrieve existing information from memory. There is little decline in the ability to store new information once it is learned (19).

Personality changes associated with aging: Whereas basic personality traits may remain rather stable throughout adulthood, relatively predictable shifts may occur in other aspects of a person's personality. One of the best documented personality changes in adulthood is an increased preoccupation with one's inner life, including greater attention to personal feelings and experiences and reduced extraversion. A second domain in which age-related changes have been reported is gender role identity. With advancing age, men and women appear to become more similar in terms of their values and personality styles. Studies in a number of different cultures have found that men tend to become more nurturing, expressive and affiliation-seeking as they grow older, whereas women tend to become more instrumental and achievement-oriented (20). Table 1 shows other physiological changes in body.

There are various theories put forward to explain the above mentioned changes of ageing. Biologic theories classify aging as genetic (heredity) and nongenetic (wear and tear). Although there are currently over 300 theories to explain the aging phenomenon, it is still not well understood why organisms age and why the aging process can vary so much in speed and quality from individual to individual (21-22). Some of the most widely accepted and major theories of aging are:

The "wear and tear" theory: It is believed that the body and its cells are damaged by overuse and abuse. The organs, liver, stomach, kidneys, skin and so on are worn down by toxins in our diet and in the environment; by the excessive consumption of fat, sugar, caffeine, alcohol and nicotine; by the ultra-violet rays of the sun and by the many other physical and emotional stresses to which we subject our bodies. Wear and tear is not confined to organs, but also takes place on the cellular level (23).

The Neuroendocrine Theory: This theory elaborates on the complicated network of biochemicals that governs the release of our hormones. The hypothalamus sets off various chain reactions whereby an organ releases a hormone which in turn stimulates the release of another hormone, which in turn stimulates yet another bodily response. Aging causes a drop in hormone production leading to decline in our body's ability to repair and regulate itself (23).

The Genetic Control Theory: This theory focuses on the genetic programming encoded within our DNA. We are born with a unique genetic code, a predetermined tendency to certain types of physical and mental functioning. The genetic inheritance has a great deal to tell about how long we live. Each of us has a biological clock ticking away set to go off at a particular time. When that clock goes off it signals our body first to age and then to die. The timing on this genetic clock is subject to enormous variation (24).

The Free Radical Theory: Free-radical are required for physiological functions, but free radicals also attack the structure of our cell membranes, creating metabolic waste products like lipofuscins. An excess of lipofuscins in the body is shown as a darkening of the skin in certain areas, so-called "aging spots." Lipofuscins in turn interfere with the cells ability to repair and reproduce themselves. They disturb DNA and RNA synthesis and interfere with synthesis of protein. They also lower the energy levels, prevent the body from building muscle mass and destroy cellular enzymes, which are needed for vital chemical processes. Free-radical disruption of cell metabolism is part of what ages our cells (21).

Substance that combats free-radical damage is known as a free-radical scavenger. Free-radical scavengers actually seek out free radicals and harmlessly bind them before they can attach themselves to other molecules and/or cause cross-linking. Specialists in anti-aging medicine prescribe a host of natural and manufactured free-radical scavengers to help combat the effects of aging (25).

Other theories of aging that have been proposed throughout the years are:

Mitochondrial Theory: The free radical theory is supported by direct experimental observations of mitochondrial aging. Mitochondria are one of the easiest targets of free-radical injury because they lack most of the defenses found in other parts of the cell. This theory



states that electrons leaking from the electron transfer chain (ETC) reduce molecular oxygen to form O_2^- (superoxide anion radicals) which can cause the generation of other reactive oxygen species (ROS). The ensuing state of oxidative stress results in damage to ETC components and mitochondrial DNA (mtDNA), thus increasing further the production of ROS. Ultimately, this 'vicious cycle' leads to a physiological decline in function or aging (6,26).

Waste accumulation theory: In the course of their life span, cells produce more waste than they can properly eliminate. This waste can include various toxins which when accumulated to a certain level and can interfere with normal cell function, ultimately killing the cell. Evidence supporting this theory is the presence of a waste product called lipofuscin. The cells most commonly found to contain lipofuscin are nerve and heart muscle cells, both critical to life (27).

Hayflick limit theory: Hayflick theorized that the aging process was controlled by a biological clock contained within each living cell. The 1961 studies concluded that human fibroblast cells (lung, skin, muscle, heart) have a limited life span. They divided approximately 50 times over a period of years and then suddenly stopped. Nutrition seemed to have an effect on the rate of cell division. Overfed cells made up to 50 divisions in a year, while underfed cells took up to three times as long as normal cells to make divisions (28).

Death hormone theory (DECO): Denckle speculated that as we age the pituitary begins to release DECO (decreasing oxygen consumption hormone) which inhibits the ability of cells to use thyroxine, a hormone produced by the thyroid. Thyroxine governs basal metabolism, the rate at which cells convert food to energy. The metabolic rate brings on and accelerates the process of aging (24).

Thymic-stimulating theory: Thymic hormones may play a role in stimulating and controlling the production of neurotransmitters in brain and endocrine system hormones. It means that they may be the pacemakers of aging itself and also the key regulators responsible for immunity. The size of this gland reduces from 200 to 250 grams at birth and then shrinks to around three grams by age 60. A number of explanations have been put forward to explain this 'thymic menopause' including the possible loss of thymic progenitors or epithelial cells, a diminished capacity to rearrange T-cell receptor genes

and alterations in the production of growth factors and hormones (29).

Caloric restriction theory: After years of animal experiments and research on longevity, Dr. Walford has developed a high nutrient low-calorie diet demonstrating that "under nutrition with malnutrition" can dramatically retard the functional, if not the chronological aging process. An individual on this program would lose weight gradually until a point of metabolic efficiency was reached for maximum health and life span. Recent studies identified a gene, SIR2, which encodes an NAD-dependent deacetylase and may mediate the effects of calorie restriction. To date, the only intervention known to delay aging is caloric restriction (30).

The cross-linking theory: This theory of aging is also referred to as the glycosylation theory of aging. In this theory it is the binding of glucose (simple sugars) to protein, (a process that occurs under the presence of oxygen) that causes various problems. Once this binding has occurred the protein becomes impaired and is unable to perform as efficiently (31).

The telomerase theory of aging: A new theory of aging that holds many promising possibilities for the field of anti-aging medicine is the telomerase theory of aging. This theory was born from the surge of technological breakthroughs in genetics and genetic engineering. Telomeres are sequences of nucleic acids extending from the ends of chromosomes. Telomeres act to maintain the integrity of our chromosomes. Every time our cells divide telomeres are shortened, leading to cellular damage and cellular death associated with aging. Scientists discovered that the key element in rebuilding our disappearing telomeres is the "immortalizing" enzyme telomerase, an enzyme found only in germ cells and cancer cells. Telomerase appears to repair and replace telomeres manipulating the "clocking" mechanism that controls the life span of dividing cells. Future development of telomerase inhibitor may be able to stop cancer cells from dividing and presumably may convert them back into normal cells (32,33).

Conclusion

It is believed that some of these theories of aging may be a result of other theories. Many of them are interlinked, in the same complex way the biological processes of the body and the many factors affecting it are linked. Despite



the monumental progress in aging research there has yet to be a unanimous vote on one specific theory of aging. Most of these theories have been disputed by scientists over and over again and many of them are very old. Age-related changes do not occur uniformly in individuals; rather they are controlled jointly by genetic and environmental factors which further heighten the difficulty of finding a universal theory. What is universal is that we are all involved in a global-aging phenomenon. Through theoretical gerontology and anti-aging medicine we may eventually discover there is no limit to human life span. Understanding the molecular mechanisms underlying the physiological ageing process may ultimately help in the understanding and prevention of age-related problems and diseases.

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