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Physiological overview of Human Ageing process

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Abstract

The impact that ageing has on organisms is a complex interaction between the processes of ageing at a cellular, organ and integrated systems level, and the effects of environmental factors such as nutrition, infection and trauma. Physiologic ageing involves changes that tend to be linear with time and are characteristically decremental in nature. A number of the functional changes can be delayed in onset or slowed in their progress by lifestyle. Aging challenges the reserves of function that allow for activity above the resting level and for regulation of the internal environment. Physiological changes occur with aging in all organ systems. The cardiac output decreases, blood pressure increases and arteriosclerosis develops. The lungs show impaired gas exchange, a decrease in vital capacity and slower expiratory flow rates. The creatinine clearance decreases with age although the serum creatinine level remains relatively constant due to a proportionate age-related decrease in creatinine production. Functional changes, largely related to altered motility patterns, occur in the gastrointestinal system with senescence, and atrophic gastritis and altered hepatic drug metabolism are common in the elderly. Progressive elevation of blood glucose occurs with age on a multifactorial basis and osteoporosis is frequently seen due to a linear decline in bone mass after the fourth decade. The epidermis of the skin atrophies with age and due to changes in collagen and elastin the skin loses its tone and elasticity. Lean body mass declines with age and this are primarily due to loss and atrophy of muscle cells. Degenerative changes occur in many joints and this, combined with the loss of muscle mass, inhibits elderly patients' locomotion. These changes with age have important practical implications for the clinical management of elderly patients.

Keywords*: ageing, physiology, senescence ,changes ,cells*

I. Introduction

Aging is inevitable, and as life expectancy increases it becomes more important to understand physiological mechanisms associated with the normal aging process so that quality of life can be sustained. Maintaining physiological function or “health” in an aging population will help to reduce the burden on the

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existing medical systems as older individuals consume medical services. Physiologists are in the ideal position to develop and test hypotheses of how genetic, molecular, and cellular mechanisms of aging affect human physiology. Aging, as an extremely complex multifactorial process, has recently replaced the earlier search for a single cause, such as a single gene or the decline of a key body system. This mini-review keeps in mind the multiplicity of mechanisms regulating aging and examines them at molecular, cellular, and systemic levels. Although several theories are identified only briefly, a few are discussed in more detail (e.g., evolutionary, gene regulation, cellular senescence, free radicals. [1] It is generally accepted that the aging process falls physiologically into three groups of changes that occur with advancing age [2]. The first group encompass changes in cellular homeostatic mechanisms, for example, body temperature, blood, and extracellular fluid volumes; the second group are related to a decrease in organ mass; the third and possibly the most important group of changes, in terms of their impact, involve a decline in and loss of the functional reserve of the body's systems. Loss of these functional reserves may impair an individual's ability to cope with external challenges such as surgery or trauma. Maintaining physiological function (health) in an aging population is of prime importance not only to the well-being of the aging individual, but also from a social perspective, helping to reduce the burden on medical services and systems [3]. It has also been long established that the physiological changes associated with normal aging are mirrored during periods of immobility, such as prolonged hospital bed rest, or after a fractured limb or a fall.

II. Theories of ageing

Many theories have been proposed to explain the process of aging, but neither of them appears to be fully satisfactory[4]. The traditional aging theories hold that aging is not an adaptation or genetically programmed. Modern biological theories of aging in humans fall into two main categories: programmed and damage or error theories. The programmed theories imply that aging follows a biological timetable, perhaps a continuation of the one that regulates childhood growth and development. This regulation would depend on changes in gene expression that affect the systems responsible for maintenance, repair and defense responses. The damage or error theories emphasize environmental assaults to living organisms that induce cumulative damage at various levels as the cause of aging.

The programmed theory has three sub-categories

1) Programmed Longevity: Aging is the result of a sequential switching on and off of certain genes, with senescence being defined as the time when age-associated deficits are manifested. Dr. Davidovic et al discuss the role of genetic instability in aging and dynamics of the aging process [4].

2) Endocrine Theory: Biological clocks act through hormones to control the pace of aging. Recent studies confirm that aging is hormonally regulated and that the evolutionarily conserved insulin/IGF-1 signaling (IIS) pathway plays a key role in the hormonal regulation of aging. Dr. van Heemst discusses the potential mechanism underlying IIS and aging process[5].

3) Immunological Theory: The immune system is programmed to decline over time, which leads to an increased vulnerability to infectious disease and thus aging and death. It is well documented that the effectiveness of the immune system peaks at puberty and gradually declines thereafter with advance in age. For example, as one grows older, antibodies lose their effectiveness, and fewer new diseases can be combated effectively by the body, which causes cellular stress and eventual death[6]. Indeed, dysregulated immune response has been linked to cardiovascular disease, inflammation, Alzheimer's disease (AD), and cancer. Although direct causal relationships have not been established for all these detrimental outcomes, the immune system has been at least indirectly implicated [7].

The damage or error theory include

1) Wear and tear theory: Cells and tissues have vital parts that wear out resulting in aging. Like components of an aging car, parts of the body eventually wear out from repeated use, killing them and then the body. So the wear and tear theory of aging was first introduced by Dr. August Weismann, a German biologist, in 1882, it sounds perfectly reasonable to many people even today, because this is what happens to most familiar things around them.

2) Rate of living theory: The greater an organism's rate of oxygen basal metabolism, the shorter its life span [8]. The rate-of-living theory of aging while helpful is not completely adequate in explaining the maximum life span [9].Dr. Rollo proposes a modified version of Pearl's rate of living theory emphasizing the hard-wired antagonism of growth (TOR) and stress resistance (FOXO) [10].

3) Cross-linking theory: The cross-linking theory of aging was proposed by Johan Bjorksten in 1942 [11]. According to this theory, an accumulation of cross-linked proteins damages cells and tissues, slowing down bodily processes resulting in aging. Recent studies show that cross-linking reactions are involved in the age related changes in the studied proteins [12].

4) Free radicals theory: This theory, which was first introduced by Dr. Gerschman in 1954, but was developed by Dr. Denham Harman[13,14], proposes that superoxide and other free radicals cause damage to the macromolecular components of the cell, giving rise to accumulated damage causing cells, and eventually organs, to stop functioning. The macromolecules such as nucleic acids, lipids, sugars, and proteins are susceptible to free radical attack. Nucleic acids can get additional base or sugar group; break in a single- and double-strand fashion in the backbone and cross link to other molecules. The body does possess some natural antioxidants in the form of enzymes, which help to curb the dangerous build-up of these free radicals, without which cellular death rates would be greatly increased, and subsequent life expectancies would decrease. This theory has been bolstered by experiments in which rodents fed antioxidants achieved greater mean longevity. However, at present there are some experimental findings which are not agreed with this early proposal. The review by Igor Afanas'ev shows that reactive oxygen species (ROS) signaling is probably the most important enzyme/gene pathway responsible for the development of cell senescence and organismal aging and that ROS signaling might be considered as further development of free radical theory of aging [15].

5) Somatic DNA damage theory: DNA damages occur continuously in cells of living organisms. While most of these damages are repaired, some accumulate, as the DNA Polymerases and other repair mechanisms cannot correct defects as fast as they are apparently produced. In particular, there is evidence for DNA damage

accumulation in non-dividing cells of mammals. Genetic mutations occur and accumulate with increasing age, causing cells to deteriorate and malfunction. In particular, damage to mitochondrial DNA might lead to mitochondrial dysfunction. Therefore, aging results from damage to the genetic integrity of the body's cells.

III. Factors of ageing

Several factors (the lengthening of the average and, to a lesser extent, of the maximum human life span; the increase in percentage of elderly in the population and in the proportion of the national expenditure utilized by the elderly) have stimulated and continue to expand the study of aging. Recently, the view of aging as an extremely complex multifactorial process has replaced the earlier search for a distinct cause such as a single gene or the decline of a key body system. This review keeps in mind the multiplicity of mechanisms regulating aging; examines them at the molecular, cellular, and systemic levels; and explores the possibility of interactions at these three levels. The heterogeneity of the aging phenotype among individuals of the same species and differences in longevity among species underline the contribution of both genetic and environmental factors in shaping the life span. Thus, the presence of several trajectories of the life span, from incidence of disease and disability to absence of pathology and persistence of function, suggest that it is possible to experimentally (e.g., by calorie restriction) prolong functional plasticity and life span.

In this review we will discuss some of the physiological changes that occur with aging in the cardiovascular, respiratory, renal, gastrointestinal, endocrine, skin and musculoskeletal systems and their consequence for various therapeutic approaches in the day-to-day management of patients. We will concentrate mostly on changes that are of clinical importance.

Cardiovascular system:

Heart

Cardiac output decreases linearly after the third decade at a rate of about 1 percent per year in normal subjects otherwise free of cardiac disease.'[16] Due to the small decrease in surface area with age the cardiac index falls at a slightly slower rate of 0.79 percent per year. The cardiac output of an 80-year-old subject is approximately half that of a 20-year-old.[17] The basis of this decrease in cardiac function is unknown but may relate to one of several factors. First, senescent cardiac muscle has a decreased inotropic response to catecholamines, both endogenous and exogenous, and, perhaps of more clinical significance is a decreased response to cardiac glycosides.' Second, with aging there is an associated increase in diastolic and systolic myocardial stiffness, perhaps due to increased interstitial fibrosis in the myocardium.[18] Third, there is a progressive stiffening of arteries with age, particularly of the thoracic aorta, leading to an increased afterload of the heart.[19] And finally, in autopsy studies as many as 78 percent of subjects older than 70 have been shown to have amyloid deposits in the myocardium, predominantly in the atria, but also in the ventricles and pulmonary vessels.[20]

Hypertension

A progressive increase in blood pressure after the first decade of life has long been regarded as a normal consequence of aging and was the basis for ignoring the presence of hypertension in the elderly. Only in

the past decade or so have prospective studies provided evidence of the grave portents of hypertension for the older age group as well as the young and the potential preventive value of early treatment? The elevation with age is more pronounced for systolic than diastolic pressure. When hypertension is defined as a systolic blood pressure of greater than 160 mm of mercury and simultaneously a diastolic of greater than 95 mm of mercury, approximately 16 percent of the general adult population is hypertensive but about 50 percent of those over age 65 are hypertensive.

Arteriosclerosis and Coronary Artery Disease

Thickening of the walls of arteries with hyperplasia of the intima, collagenization of the media and accumulation of calcium and phosphate in elastic fibers progressively occurs with aging. In addition, the lipid content of nonatherosclerotin portions of vessels increases, particularly of cholesterol. [21] Although none of these age-related changes has definitely been shown to be a precursor of arteriosclerosis, atherosclerosis clearly increases with aging. Raised fibrous plaques that contain lipid, atheromas, of the abdominal aorta increase linearly from onset at about age 20 to reach approximately 30 percent by -age 70. In general, atherosclerosis occurs earlier in the aorta and carotid arteries than in the coronary and cerebral arteries and peripheral vascular disease appears later. Myocardial infarction from coronary artery disease increases dramatically with age and although many risk factors are known, age itself is probably the most significant. Prevention at present is aimed at amelioration of the other factors, such as hypertension, obesity and cigarette smoking.

Respiratory System

Lung Volume

A linear decrease of vital capacity is found that amounts to a decrement of about 26 ml per year for men and 22 ml per year for women starting at age 20. The total lung capacity remains constant, however, and thus the residual volume increases with age. The ratio of residual volume to total lung capacity (RV/TLC) is about 20 percent at age 20 and increases to 35 percent by age 60, with most of this increase in RV/TLC occurring after age 40. [22]

Flow Rates

There is a 20 percent to 30 percent decrease in maximum voluntary ventilation, forced expiratory volume in one second, maximal expiratory flow rate and maximum midexpiratory flow during adult life. [23] The basis for these changes is not known but again may relate to a decrease in the elastic recoil properties of the lung. This would result in both a decreased ability to generate normal expiratory pressures as well as increased resistance to expiration due to abnormally early airway collapse.

Infections

It is well known that elderly patients have a pronounced increase in incidence of pneumonia, both bacterial and viral, compared with younger persons. Although much of this may be due to a general depression of immune system function, other more specific factors may play a role. Pneumonia generally results from aspiration of oropharyngeal secretions and such aspiration appears more frequent in the elderly. Perhaps of even greater importance, the normal mechanical clearing of the tracheobronchial tree by the mucociliary apparatus is significantly slower in nonsmoking older persons than in their younger counterparts. Finally, due perhaps to

poor oral hygiene, decreased flow of saliva or difficulty with swallowing, older persons have a higher rate of colonization of their oropharynx with Gram-negative bacilli than do younger persons.

Genitourinary sytem:

Kidneys

A gradual decrease in the volume and weight of the kidneys occurs with aging so that by the ninth decade renal size is about 70 percent of that of the third decade. Moreover, there is a decline in the total number of glomeruli per kidney from about 1,000,000 below the age of 40 to about 700,000 by age 65.[24,25] With the reduction in the number of glomeruli there is a concomitant age-related decrease in the creatinine clearance.

Bladder

Urinary incontinence has been found in 17 percent of men and 23 percent of women older than 65 years.'[26] In about half of the women and a fifth of the men this was due to stress incontinence alone. The capacity of the bladder decreases with age from about 500 to 600 ml for persons younger than 65 to 250 to 600 ml for those older than 65. Perhaps more important, in younger persons the sensation of needing to void occurs when the bladder is little more than half filled but in many who are older the sensation occurs much later or sometimes not at all, leading to overflow incontinence. These changes appear to be due more often to central nervous system disease than to bladder dysfunction.

Prostate

Enlargement of the prostate occurs in most older men; by age 80 more than 90 percent of men have symptomatic prostatic hyperplasia with varying degrees of bladder neck obstruction and urinary retention. Prostate surgery is required in 5 percent to 10 percent of all men at some time. Recently the cause of the hyperplasia has been more clearly defined; the concentration of dihydrotestosterone (DHT) increases in prostatic cells. [27] The increase in the intraprostatic concentration of DHT is due to two age-related changes: an estrogen-mediated enhancement of androgen receptors on prostatic cells as well as a decrease in the intracellular catabolism of DHT.

Gastrointestinal system

Esophagus

Age-related changes of esophageal function, socalled presbyesophagus, are due primarily to disturbances of esophageal motility. The esophagus in an older person may have a decreased peristaltic response, an increased nonperistaltic response, a delayed transit time or a decreased relaxation of the lower sphincter on swallowing. The decrease in peristalsis and delay in transit time may lead to dysphagia with a voluntary curtailment of caloric consumption. Nonperistaltic contractions are found almost exclusively in the elderly.

Stomach

The incidence of atrophic gastritis increases significantly with age. In a Scandinavian study approximately 40 percent of apparently healthy subjects older than 65 had evidence of atrophic gastritis. [28] At present, atrophic gastritis is divided into type A which is confined to the body and fundus sparing the antrum

and type B which is associated with atrophy of both antral and fundic glands. Both types increase in frequency with advancing years. Both types of atrophic gastritis are premalignant lesions.

Colon

A decrease in intestinal motility occurs with age. The colon becomes hypotonic, which leads to increased storage capacity, longer stool transit time and greater stool dehydration. These are all etiologic factors in the chronic constipation that plagues the aged. Laxative abuse therefore results and is the most common cause of diarrhea in the elderly. A high-fiber diet is the treatment of choice and this can best be achieved by prescribing a diet rich in bran.

Liver and Biliary Tract

The liver decreases in weight by as much as 20 percent after the age of 50 but perhaps because of its large reserve capacity this attrition is not reflected by a decrease in the usual liver function tests. Although tests of liver function show little or no change with age, a large number of drugs such as diazepam and antipyrine are known to be metabolized more slowly by the liver in the elderly. This alteration in hepatic drug metabolism may be due to a decrease in the appearance, amount or distribution of the smooth endoplasmic reticulum. Biliary tract disease is unusual before the third decade and the incidence of cholelithiasis increases greatly with age.

Endocrine system

Menopause

Nowhere are the development of age-related changes more apparent than in the human female climacteric. Menopause occurs because of the disappearance of oocytes from the ovary through ovulation and atresia. Little is understood about the process of ovarian atresia and whether it is due to primary ovarian failure or secondary to hypothalamic-pituitary changes. Several consequences of the menopause deserve mention. First is the vasomotor instability or hot flashes. Two thirds to three quarters of menopausal women will experience flushing, with 80 percent having the symptoms for longer than one year and 25 percent to 50 percent for more than five years. Changes in skin temperature, skin resistance, core temperature and pulse rate occur during the flush. Besides being a major disturbance while women are awake, the hot flashes may occur during sleep, leading to waking episodes. Insomnia with possible physiologic and psychologic disturbances may thus result.

Osteoporosis

Osteoporosis is a skeletal disorder characterized by a decrease in bone mass which may result in mechanical failure of the skeleton. The decrease in bone mass is an age-related phenomenon. Beginning in the fourth decade there is a linear decline in bone mass at a rate of about 10 percent per decade for women and 5 percent per decade for men. Thus, by the eighth and ninth decades 30 percent to 50 percent of the skeletal mass may be lost. The decrease in bone mass is due to a relative increase of bone resorption over formation but the basis of this is unknown. Low-dose estrogen therapy GERIATRIC MEDICINE can arrest or retard bone loss if begun shortly after the menopause. [29,30]

Skin

Epidermis

Atrophy of the epidermis occurs with age and is most pronounced in exposed areas: face, neck, upper part of the chest, and extensor surface of the hands and forearms. In addition to the thinning of the epidermis there is notable flattening of the dermal epidermal junction with effacement of both the dermal papillae and the epidermal reti pegs. The turnover rate of cells in the stratum corneum decreases with age and in persons older than 65 it takes 50 percent longer to reepithelialize blistered skin than in young adults. The decrease in epidermal cell growth and divisioncausally contribute to the increased incidence of decubitus ulcers in older patients. [30]

Dermis

Dermal collagen becomes stiffer and less pliable with age; elastin is more cross-linked and has a higher degree of calcification. These changes cause the skin to lose its tone and elasticity, resulting in sagging and wrinkling. [31]

Musculoskeletal system

Muscle

The age-dependent decline in lean body mass is well known and is primarily due to loss and atrophy of muscle cells. Some muscles, such as the diaphragm, show few if any changes while others, such as the soleus, show pronounced infiltration by collagen and fat.[32] Age-related changes also occur in the innervation of muscle but the exact pathologic process is not well understood.

Skeletal

Degenerative joint disease occurs in 85 percent of persons older than 70 years of age and is a major cause of disability. It affects both the peripheral and axial skeleton and is characterized by degeneration of cartilage, subchondral bone thickening and eburnation, and remodeling of bone with formation of marginal spurs and subarticular bone cysts. Due to its predilection for weight-bearing joints, wear-and-tear type mechanisms must be operative. When the degenerative changes are pronounced, pain can be severe, greatly limiting the activity status of an elderly patient. Fortunately, adequate drug and surgical treatments exist but old people are truly restricted by their joints.

IV. Conclusion

Quality of life is becoming a valuable outcome measure in clinical trials and in the decision-making process for medical interventions. Although aging is inevitable, understanding the basic physiology of aging processes can contribute to decision making that can help to sustain quality of life in an aging population.

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