

Physiological Modification, Longevity, Mechanism of Ageing and its prevention

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Abstract

In spite of decades of research, ageing has proved to be an almost inevitable process. The only organisms which do not grow old and never die are the unicellular organisms. In humans, sperm and ova get the genetic qualities which are transferred to their off-springs thus probably maintaining the qualitative immortality chain. Physiological, pathological, psychological, social, environmental, economical and nutritional factors influence the ageing process. So, not everyone ages with the same speed and in the same manner. The combination of declining fertility and increasing life expectancies is a major problem for most of the developing and developed countries. The economic, social and health status of the fast growing elderly population poses a great challenge. The elderly (more than 60 years) comprises 7.5 percent of Indian's total population. Ageing is characterized by progressive, irreversible changes in different body systems leading to impaired ability of an individual to external or internal stress. For understanding, the mechanism of ageing, various theories are considered like- free radical, glycation, genetic, mitochondrial mutation, hormone based ageing, telomerase theory of ageing. Balanced diet including high fiber content with adequate vitamins (A, B, C, D, E, folic acid), minerals and caloric restriction may prove helpful for delaying ageing. Proper physical exercise, good life style, good stress management and medications including hormonal therapy increase the work capacity and can postpone ageing.

INTRODUCTION

Ageing is highly complex and heterogeneous process with numerous dimensions attached to it. The process of ageing be it physiological or pathological is inevitable. So, growing older is not, in and or itself, a crises. Life is punctuated by normal points of transition, and old age includes many normative changes with which each person must cope.

Physiological, psychological, social, economical and to some extent cultural and educational factors - all determine the expression altitude and

behavior of a man and thus influence the quality of ageing. Not every one ages with the same speed and in the same manner. Biologically 70 years old may be quite physically fit and psychologically happy, but a 40 year old may show early sign of ageing (**premature ageing**). This occurs predominantly in societies, which are developing and are still grappling with problems of malnutrition, poverty, illiteracy, insanitation and chronic sequels of disease. This can result in shorter life span of poor quality and is likely to happen more in areas with these limitations eg. in villages and urban slums. In urban areas, on the other hand, individualism grows, relations between different generations come under stress, feeling of loneliness ensues even in their own homes and unavailability of women due to their deployment in job market, is on rise. From a social angle, ageing falls to an entirely realm of notion.

Starting from young to very old subjects, ageing is associated with progressive remodeling. Such an age dependent remodeling process mainly affects anthropometrics, endocrine and thus, also metabolic factors, researchers in Nepoli, Italy reports (1).

"Interestingly, it occurs in some individuals successfully, while in others unsuccessfully. Centenarians in good health conditions are a very selected group of subjects representing an exceptional condition. Why the centenarians reach the extreme human life span (**Longivity**) is still unknown", wrote M. Barbieri and colleagues, University of Naples (2).

Some gerontologists prefer to use of word **senescence** because "ageing" implies that the passage of time necessarily results in deterioration (biological entropy) - which is certainly not true during the early developmental time of life (before the age of 10 or 12 years in humans). The term **geriatric** stems from the Greak 'geras' (old age) and 'iatros' (physician) and thus refers to treating or healing older people. While, inclusion of geriatric medicine was accepted in medical curriculum in 1978.

While **Frailty** identifies older persons at increased risk of morbidity and mortality. However, it continues to be ill defined in medical literature. Its concept underlines some common concerns of older people.

1. Being dependent on others or at a substantial risk of dependency.
2. Experiencing the loss of physiological reserves.
3. Experiencing detachment from the environment.

4. Having many chronic illness.
5. Having complex medical and psychosocial problems.
6. Having atypical disease presentations.
7. Experiencing accelerated ageing.

Frailty was defined by Campbell and Buchner as a condition or syndrome which results from multi-systematic reduction in the reserve capacity to the extent that a number of physiological system are close to or past the threshold of symptomatic clinical failure (3).

Rockwood et al, proposed that the state of health in old age in like a beam balance, balancing the health assists and deficits (4). Lipsitz, et al have constructed frailty in the model of mathematical chaos theory suggesting that frailty occurs when the responses of an organism, lose complexity in resting dynamics and show maladaptive response to perturbations (5). Bortz uses the concept of symmorphosis which describe how different body structures and function co-adjust to different levels of organismic energy flow and suggests that frailty is a result of early disease in multiple systems leading to impaired muscle strength, mobility, balance and endurance (6).

Biochemical features of frailty: It is likely that the manifestations of the primary or underlying disease would also be easily visible in frail order patients. Various biochemical abnormalities observed in frail older subjects are :

- Increased blood levels of catabolic cytokines : C-reactive protein, IL-6.
- Elevated markers of blood coagulation : D-dimer, factor VIII.
- Reduced hemoglobin levels : normocytic subclinical anemia.
- Reduced hormonal levels : growth hormone, insulin like growth factor - 1 (IGF-1), testosterone (in men), dihydroepiandrosterone (DHEA) and estradiol (in women).
- Increased hormonal levels : cortisol (especially postmenopausal women); lutenizing hormone (in men).
- Decreased carrier protein levels : transthyretin, retinol binding protein, albumin.

Demographic Trends : Throughout the world the number and proportion of the aged population (age 60+) is increasing because of the combined effects of **increasing longevity and declining fertility** in different parts of world (7).

Still there are large differences in the regional patterns of ageing. The median age of the world's population increases from 26.6 years in 2000 to 37.3 years in 2050 and then to 45.6 years in 2100, when it is not adjusted for longevity increases. When increases in life expectancy are taken into account, the adjusted median age rises from 26.6 in 2000 to 31.1 in 2050 and only 32.9 in 2100, slightly less that what it was in China region in 2005 (8).

Though population ageing is already a major problem for most of the developed countries in the world, it is rapidly emerging as a major social and economical issue in developing countries, as well. While population ageing is a success story of socioeconomic development and good public health practice, it has also lead to economic and social crisis due to crumbling support system, with increased demand for health and welfare services. The increasing number of older people also in Indian society has been well perceived. The elderly (people above the age of 60 years) comprises 7.5 percent of Indian's total population, and making health care available and accessible to them is one of the health priorities of the country (9).

PHYSIOLOGICAL MODIFICATION

Ageing is characterized by overall progressive decline in the organism's capacity for adaptation and it is inevitable. Physiologically, ageing refers to the impaired ability to maintain homeostasis in the face of external or internal challenges or stresses. Age related changes are observed in both cellular level and gross level. The age related changes are broadly decreased capacities of different organ, decreased tolerance and decreased reserved. Body Weight is also declines after age of 55, due to loss of lean tissue, water and bone. The body system changes with ageing are mentioned below:-

Blood: Haemopoietic marrow is gradually replaced by fatty marrow as age advances (after age of 60). This occurs first in long bones and then in flat bones. The last bone to be affected is the vertebrae. Therefore,

physiological reserve capacity for erythropoiesis and leucopoiesis is possibly reduced in the elderly.

Immune Mechanism: There is a decline in immunocompetence in both cell mediated and humeral immunity. It makes the elderly more susceptible to infection and autoimmune disease.

Muscles: Muscle weakness, wasting, fatigue, inactivity, slow and/or unsteady gait, exercise de-conditioning, functional deficit in multiple domains resulting in frequent falls, decline in mobility is observed. Also increased reaction time, decreased muscle strength and impaired mobility reduce the scope and speed activities that are possible for the elderly.

Respiratory System: Microscopic structure shows decline in the respiratory functions. The alveoli become flatter and shallower. There is reduction in the vital capacity and also decreased compliance of the lung tissue by the age of sixty. The chest wall also becomes rigid.

Cardiovascular: As age advances there is atherosclerosis and this leads to ischemic heart disease and hypertension. Elasticity of the arterial wall is reduced. The myocardium shows atrophic changes. Structural change also takes place in the valves.

Alimentary Canal: There is wear and tear of teeth due to loss of enamel, loss of dentine and loss of cement. Teeth become prone to caries and periodontal disease. There may be weakness of the pharyngeal muscle leading to difficulty in swallowing. There is also age related mucosal atrophy. Number of hepatocytes may also reduce.

Excretory System: Normally, intake of protein diet causes increase in renal solute load. This in turn tends to cause chronic renal vasodilatation and high renal capillary pressure. There is extravasation of macromolecules in glomeruli and mesangial reaction. This way lead to progressive glomeruli sclerosis and in long run there may be impaired renal function as age advances. There may be decrease in number and size of nephrons and also reduction in the weight of kidneys. Urinary incontinence is also observed.

Endocrine System: As age advances blood concentration of hormones is also decreases. There is decreased responsiveness to hormones. It is observed that in an aged person there is decrease response to stress of the hypothalamic hyperphyseal axis.

In females there is decreased estrogen and progesterone level after menopause. There is also reduced sensitivity to growth factors and hormones due to fewer receptors and dysfunctional post receptor pathways.

Nervous System: Loss of memory and loss of ability to learn is occurs with advanced age (impaired cognition). The brain losses about 20% of its weight around the sixth decade. Thermoregulation deteriorates; thus old persons loss their ability to fight extremes of environmental heat or cold. As the normal brain ages, changes occur with respect to the synthesis, turnover and receptor binding of neurotransmitters. Level of norepinephrine, serotonin, dopamine, gamma-aminobutyric acid (GABA), and acetylcholine decreases. Thus result in increased sensitivity of receptor site in the areas of the brain associated with mood, cognition, coordination, anxiety and depression in response to stress. Insomnia, reduction in REM (Rapid Eye Movement) sleep and other sleep problems in elderly people may occur as a result of physiological changes that affect patterns of sleep.

Special Sense: Progressive loss of hearing (particularly for higher frequencies), smell and taste of salt & bitter (sweet & sour are much less affected) is occurs as age advances. In most of the elderly people presbyopia and cataracts develops, leads to decreased visual acuity, peripheral vision, and night vision may restrict the activity of older persons, which may contribute to lowered self esteem and depression. Decreased auditory acuity, speech perception and auditory discrimination may also hamper social interaction.

MECHANISM OF AGEING

Ageing is a syndrome of changes that are deleterious, progressive, universal and thus far irreversible. Ageing damage occurs to molecules (DNA, proteins, lipids), to cells and to organs. Attempts to classify theories of ageing have led to the two major classifications **programmed ageing and wear & tear ageing**. Programmed ageing would be due to something inside an organism's control mechanisms (genes) that forces elderliness and deteriorations. By contrast ageing due to wear & tear is not the result of any specific controlling program, but is the sum effect of many kinds of environmental assaults i.e., damage due to radiation, chemical toxins, metal ions, free-radicals, hydrolysis, glycation, disulfide-bond cross-linking etc. Such damage can affect genes, proteins, cell membranes, enzyme function, blood vessels etc. There are many theories regarding the cause of sensility.

1. **Free Radical theory-** Oxidative stress ensues when large amount of reactive oxygen species are produced in the cells, that can evade or overwhelm the antioxidant protective mechanism of cells and tissues, and produce major interrelated impaired cell metabolism including DNA strand breakage, rise in intracellular free Ca^{2+} , damage to membrane ion transporters and other specific proteins leading to cell death (10).

Prime target to free radicals attack are the polyunsaturated fatty acids in the membrane lipids, causing lipid peroxidation, which has been found to be a major event in the production of pathophysiological alterations in elderly (11). These lipid peroxide (malion aldehyde) bind to membrane protein may alter their function, toxicity, permeability, rigidity and integrity and thereby may induce culprit effect on electrolyte imbalance leading to the progression of ageing progress (12).

Garg and Sanchette have well elucidated that role of various ion channels in CVD (Cardiovascular disease), CNS (Central nervous system), taste sensation, skeletal muscle, renal, respiratory, pancreatic, erectile and platelet functions. Inactivation of these ion channels may produce physical and functional disability with age (13).

The total antioxidant activity including co-operative action of other non-enzymatic antioxidants such as vitamin C, E, A, uric acid and albumin may have a significant role in the physiochemical alterations during ageing. Vit C, an exogenous water soluble antioxidant, plays a key role in protecting plasma lipids against peroxidation, collagen synthesis, wound healing and improving vascular endothelium dependant vasodilatation (14). Vitamin E, mainly α -tocopherol, is the most potent lipid soluble chain breaking antioxidant which has been theorized to extend life span, enhance cell mediated immunity in elderly people and prevent age related functional decline and diseases (15).

2. **Glycation Theory-** Proteins can be damaged both by free radicals and by glycation. Glycation (also called the Maillard reaction or non-enzymatic glycosylation) is a reaction by which reducing sugars become attached to protein without the assistance of an enzyme. Advanced Glycation End Products (AGEs) increase the rate of free radical production to 50 times from proteins. AGEs attached to LDL-cholesterol accelerates oxidation and subsequent atherosclerosis. The irreversible cross-linked proteins of AGEs in vessel collagen also contribute to

atherosclerosis, as well as to kidney failure- conditions worsened in diabetes (16). Cataracts are composed of urea-soluble proteins in the lens of the eye. AGEs aggravate protein cross-linking in the plaques and tangles of **Alzheimer's Disease**, thereby accelerating neuron death (17).

The higher glycation rate in diabetics is greatly accelerated aging. Haemoglobin glycation is often used as a time-integrated measure of blood glucose levels in diabetics. AGEs are universal symptoms of aging adversely affecting skin, lungs, muscles, blood vessels and organ-function in general.

3. **Genetic Theory**- Some animals live for short life span and human live for a long period is thought to be determined by genetic factors. The genetic programme may be responsible for varying longevity of different person also. Some people become old at an early age known as progeria, which is also thought to be determined by genetic factors. Recent findings experimentally link DNA damage and organism aging. Longevity-regulating genetic pathways respond to the accumulation of DNA damage and other stress conditions and conversely influence the rate of damage accumulation and its impact for cancer and aging, Scientists in Netherlands reports (18). Mice and other mammals have distinct insulin and Insulin Like Growth Factor-1 (IGF-1) receptors, but the defects of either of these receptors have been shown to result in a lifespan increase for mice. Insulin resistance is associated with diabetes and is even recommended as a biomarker of aging- so it is mysterious why blocked insulin signaling can extend lifespan. Fat- Specific Insulin Receptor Knock-Out (FIRKO) mice have reduced fat mass, normal calorie, intake and an increased maximum lifespan of 18% (19). Yet deletion of all insulin receptor genes in mice results in neonatal death (20).
4. **Mitochondrial Mutations (Biosingularity)** : Researchers have discovered a new mechanism of genetic mutation in the powerhouses of our cells - mitochondria - appear to trigger cells to die and speed up the ageing process. "The mitochondrial gene basically functions as a spell-checker during the copying of mitochondrial DNA", Geneticist Tom Prolla and his group at the University of Wisconsin - Madison explains. So they altered two bases in the gene and made it defective, so that it can no longer function as a spell-checker. So as a result of that the mitochondrial DNA accumulates mutations. Because our mitochondria also control the natural process of cell death within the body, mistakes

by the spell-checking gene causes cell to commit suicide (apoptosis). "As mitochondrial mutations accumulates - and we know they accumulate with age in a number of species including human - we start observing Increased level of cell death and as a result of that we see the ageing characteristics", explains Prolla (21).

What it does mean is that cell death is likely a major factor in ageing. People also have linked free radical production to ageing, decreased immune function with ageing and other factors. Prolla explains, there's probably a set of genes which function to prolong life and to inhibit the effects of mitochondrial mutations.

Caloric restriction is the only proven way to extend life span in animals. "So if you eat less you will live longer". It's not known how caloric restriction retards ageing, but what has been observed is that there is less mitochondrial mutations in animals in caloric restriction and also less programmed cell death in some tissues (22). A unknown mechanisms is also involved in the reduced risk of disease associated with caloric restriction are of great interest and might postpone all age-related disease simultaneously (23).

Caloric restriction is not so easy to implement in people. Few people would want to restrict their calories more then ten percent, while most people would not want to restrict them at all ! So if we can understand the genes involved in the actions of caloric restriction we could probably develops drugs or nutritional therapies that might function like caloric restriction.

5. **Hormone Based Ageing Mechanism** : A number of hormones, including growth hormone, testosterone, estrogen and progesterone, have been shown in clinical trials to improve some of the physiological changes associated with human ageing (24). The mechanism begins in the brain with a mutant gene that suppresses the release of hormones that prompt rapid ageing. It appears that ageing is hormonally regulated, with a brain-based pathway that affects general hormones that come from pitutary-like system. In the brain, an important ageing function is taking place, which plays a powerful role in the rest of the body. In recent animal studies suggest that the use of growth hormone could have a life-shortening effect (25). The juvenile hormone deficiency, which results from mutation in the insulin - like receptor pathway, is sufficient to extend life span said Tatar, Assistant Professor of Ecology

and Evolutionary Biology. In flies and worms, and probably in humans, insulin like compounds mediate ageing by either retarding growth or by activating specific endocrine tissue to release other hormones (26).

6. **Telomeres and Ageing** : Telomeres, the repeated sequence found at the ends of chromosomes, shorten in many normal human cell with increased cell division. Statistically, older people have shorter telomeres in their skin and blood cells than do younger people (27). In the animal kingdom, though, long lived species often have shorter telomeres than do short - lived species, indicating that telomere length probably does not determine life span (28). Solid scientific evidence has shown that telomere length plays a role in determining cellular life span in normal human fibroblasts and some other normal cell types (29). Increasing the number of times a cell can divide, however, may predispose cells to tumor formation (30).

PREVENTION

No known substance can extend life, but the chances of staying healthy and living a long time can be improved by preventive health practices such as healthy diet, daily exercise, stress managements, control of lifestyle habits such as smoking and drinking, can lengthen the life span and improve the quality of life as people age. The methods of prevention of ageing is listed below :

1. **Physical exercise** (Check with a doctor before starting an exercise programme).
 - Aerobic conditioning : At least 20 minutes of physical activity achieving 50-75 percent of target heart rate three times per week. The best example of such an exercise programme is brisk walking which older adults can easily perform.
 - Flexibility / Stretching training : This includes at least 15 seconds of static stretching per muscle group daily.
 - Balance training : Though, there is no standard balance training exercise available, some of promising activities include yoga-asanas, dancing etc.
2. **Nutritional Supplements** : Good nutrition (balanced diet) can prevent many of the contributors of frailty which include osteoporosis, malnutrition and obesity. Evidence suggests that diet with following

modifications have substantial influence in reducing the risk of the morbidity and frailty.

- Low Fat : less than 30 percent of calories and less than 10 percent derived from saturated fats.
 - Low Sodium : Maximum of 5 gm sodium (Because of a decrease in sense of taste, older people often increase their intake of salt, which can contribute to high blood pressure and nutrient loss.
 - Low Sugar : Use of sugar is also increased in older people. Seaweeds and small amounts of honey can be used as replacements.
 - High intake of fluids : Drinking of plenty of fluids aids in maintaining healthy skin, good digestion and proper elimination of wastes. Up to eight glasses of water should be consumed daily, along with plenty of diluted fruits and vegetable juices and fresh fruits and vegetables with high water content.
 - High Calcium : 1200 mg calcium.
 - High Vitamins and Minerals : Consumption of high quality multivitamin is recommended. Common nutritional deficiencies connected with ageing include vitamins B, A, D, E and C, folic acid, calcium, magnesium, zinc, iron, chromium and trace minerals. Since stomach acids may be decreased, it is suggested that the use of a powdered multivitamin formula in gelatin capsules be used, as this form is the easiest to digest. Such formulas may also contain enzymes for further help with digestion. Common antioxidants supplements vitamin A, C and E is advisable.
 - High fiber diet is recommended, such as whole grains, freshly juiced fruits and vegetable and creamed cereals.
3. **Caloric Restriction (CR)** : The only known method that might be able to delay human ageing. Caloric restriction simply means a diet with fewer calories that still delivers the required nutritional contents. Experiments have shown longevity increases of more than 50% in certain mammals and other beneficial secondary effects, but most people find it hard to stick to such a diet.
 4. **Medications** : For the most part, doctors prescribe medications to control the symptoms and disease of ageing. A few of those antiageing drugs are Procaine, Deanol, Deprenyl, Levodopa, phenformin and

Phenytoin. The most common drugs used by the elderly are pain killer, sedatives, cardiac drugs, antibiotics and mental health drugs.

Among the common conditions which are amenable to treatment easily are : anemia of chronic disease or renal disease with erythropoietin, relief from pain and thereby muscle wasting by analgesics and physiotherapy, vitamin D deficiency by supplementation and treatment of depression with selective serotonin reuptake inhibitors.

5. **Hormonal Therapy** : Many hormones level go down with age. Assuming these hormonal changes is important in ageing. The most famous of these involve human growth hormone (HGH), used as an antiageing treatment and some evidence suggests it has beneficial effects on elderly people despite possible side effects. Other hormones whose production is decrease with age are DHEA and melatonin. DHEA improves the memory, immune system, muscle mass, sexual appetite and benefits to skin. Recently, a study claimed that melatonin level do not decrease with age per se; although due to disease or drugs, elderly persons can have low levels of melatonin.

The Estrogen Replacement Therapy (ERT) is most commonly prescribed to postmenopausal women for symptoms of ageing. It is often used in conjunction with progesterone. ERT functions is to keeps bone strong, reduced risk of heart disease, restore vaginal lubrication, and to improve skin elasticity. Evidence suggests that it may also help to maintain mental functions.

Besides these a person must have to pursued the following instructions :

- Got regular health check up.
- Practice safely habits at home to prevent falls and fractures. Always wear your seat belt.
- Stay in contact with family and friends. Stay active through work, play and community.
- Avoid over-exposure to the sun and cold.
- Keep personal and financial records in order to simplify budgeting and investing. Plan long term housing and money needs.
- Keep a positive attitude towards life. Do things that make you happy.

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