The Physiology of Ageing

Dr Adalbert Ernst

UCT Dept of Anaesthesia & Perioperative Medicine

Introduction

The development of sexual reproduction in eukaryotic cells over a billion years ago had a payoff: once two organisms had combined their genetic material to produce offspring, they were, evolutionary speaking, disposable, and there was no need to preserve individuals indefinitely once they had passed on their DNA. As such, the progressive decline in physiological function that eventually results in death is a normal phenomenon present in complex multicellular lifeforms. *Homo sapiens*, despite being one of the longest-lived of all mammals, is no exception.

These notes will concentrate on the key physiological changes that occur as humans age.

What Is Ageing?

Ageing represents *an accumulation of changes in an organism over time, manifesting as an incremental fall in physiological performance that eventually results in total loss of function (death)*. In humans, this encompasses not only physical but also psychological and social factors. It is thought that one of the reasons humans are relatively long-lived is that we have a complex social structure that is not merely dependent on passing on DNA. Indeed, longitudinal studies have shown that individuals with active social bonds and meaningful relationships live longer than those who do not.

Senescence refers explicitly to the **biological** processes involved in ageing.

Cellular senescence describes the process whereby cells lose the ability to undergo mitosis. (Normal human cells lose the ability to divide after roughly 50 generations, the so-called Hayflick Limit).

Frailty refers to the increased vulnerability to adverse outcomes as a consequence of ageing.

Theories of Ageing

There is no single unified theory of ageing. Even within the same species, different organisms will age at different rates. The current view is that ageing is a **heterogeneous** process of **gradual physiological decline**, resulting from an interplay of various mechanisms at molecular, cellular, organ, and systemic level. This is further influenced by environmental and epigenetic factors such as nutrition, infection, and trauma.

Broadly speaking, there are two major schools of thought regarding ageing.

a) The **programmed theory** of ageing supposes that, over time, there is a specific and predictable decline in homeostasis and natural defence mechanisms encoded into the genome and influenced by epigenetic factors.

b) The **error theory** proposes that the body undergoes progressive damage due to various environmental insults, particularly due the production of reactive oxygen species (ROS).

The key elements involved can be summarized as:

1. Progressive reliance on homeostatic reserves (“homeostenosis”)
2. Reduced redundancy of function (reduced reserve)
3. Impairment / reduction in repair mechanisms

Proposed molecular mechanisms involved in ageing

A clear understanding of the molecular mechanisms involved remains elusive and is thought to be an interplay of several factors, including:

Telomere shortening
Telomeres are repeated nucleotide sequences that “cap” each end of a chromosome, protecting it from damage. In most human cells, telomere length reduces with each division, because the enzyme responsible for replacing the lost ends of telomeres (“telomerase”) falls to suboptimal levels, eventually becoming unexpressed. The telomere hypothesis of ageing points out that many age-associated changes are caused by cellular senescence induced by crucially shortened telomeres.

Oxidative stress
Reactive oxygen species (ROS) such as singlet oxygen and hydrogen peroxide, generated during mitochondrial energy production, cause damage to DNA, proteins, and lipids. Superoxide dismutase (SOD) is a free-radical scavenger. There is evidence that SOD activity is increased in some long-lived organisms. Caloric restriction is known to result in longer life, reflecting reduced ROS production from decreased metabolism. Furthermore, the amino acid cysteine is essential for regenerating glutathione, one of the so-called “master antioxidants”. There is some evidence that a cysteine rich diet or even n-acetylcysteine supplementation may attenuate oxidative stress by ensuring optimal glutathione levels.

DNA damage
DNA may be damaged due to oxidative stress (see above). This includes damage to both nuclear and mitochondrial DNA (mt-DNA). The very act of DNA replication may also introduce errors into the cellular milieu with missense or nonsense mutations resulting in chain termination, or, occasionally, productions of abnormal peptides or proteins which may contribute to structural macromolecular changes.

Tumour suppression as a cause of ageing
There is growing evidence that cancer and ageing may represent two sides of the same coin. Malignancy is held in check by inbuilt, cellular tumour-suppressing mechanisms that limit unregulated cell division. However, these anti-cancer pathways also drive cellular senescence and apoptosis, which may influence age-related decline. The p53 pathway is a particularly crucial suppressor of malignant change in multicellular organisms and it is thought it actively promotes cellular senescence to prevent cancer. Animal and in vitro models have shown that increased p53 activity leads to phenotypes consistent with accelerated ageing.

Stem cell depletion
An attractive hypothesis is that stem-cell depletion in mitotically active tissues leads to ageing. This theory posits that many of the processes described above (DNA damage, telomere shortening, and mitochondrial dysfunction) result in widespread stem-cell depletion, resulting in decreased regenerative ability.

Reactivation of Developmental Programmed Senescence (DPS)
DPS is a recently discovered pathway that is distinct from the senescence induced by tumour suppression, and is active in developing embryonic tissue. It is normally self-limiting, does not involve tumour suppressor genes, and is considered essential to normal embryonic development. However, there is in vitro evidence that DPS may be induced or “switched on again” by increased levels of cytokines such as TGF (transforming growth factor) in an inflammatory milieu.

Epigenetic factors
One should not forget about the external environment! The effects of lifestyle (diet, exercise, habits, and exposure to toxins) have a significant impact on physiology. Exercise increases free-radical scavenging ability, while smoking is known to accelerate ageing by depleting telomere length.

Gender
It is well known that women generally live longer than men, even when accounting for behaviour and habits. This may be to a variety of reasons: (1) As males only have one X chromosome, they lack a backup chromosome that can be referenced during DNA repair during cell replication. (2) Testosterone is a relatively pro-oxidant hormone compared to oestrogen, and induces inflammatory changes in tissue, particularly during puberty. (3) There is even speculation that the heart-rate increase that occurs during the menstrual cycle induces metabolic adaptation equivalent to moderate exercise.

Other theories
Growth Hormone: There is some evidence that reduced growth hormone (GH) signalling correlates with increased lifespan (in mice) despite claims that GH supplementation may prolong life.
IGF-1 signalling: Long-lived mice and mice subjected to dietary restriction have reduced insulin and insulin-like growth factor (IGF-1) levels, and there is evidence for a genetic mechanism whereby increased insulin sensitivity confers longevity (independent of the negative effects of increased insulin resistance e.g. diabetes)

KEY PHYSIOLOGICAL CHANGES INVOLVED IN THE AGEING PROCESS

Cardiovascular System

The chief changes involve impairment of mechanics and contractile efficiency:

1. Arterial wall thickening, increased smooth muscle tone, and changes in the vascular matrix (loss of elastin and collagen) lead to “stiffening” or rigidity the vessels (especially large, elastic arteries)
2. This, in turn, results in elevated systolic arterial pressures, increased systemic vascular resistance (SVR), and increased afterload.
3. Cardiac work and oxygen demand increase.
4. Isolated systolic hypertension is common. Left ventricular hypertrophy (LVH) with narrowing of the left ventricular outflow tract (LVOT) may result as the left ventricle contracts more forcefully into the stiffened aorta.
5. Hypertrophy of cardiac myocytes occurs secondary to increased afterload, lengthening contraction time.
6. Occult diastolic dysfunction is common due to delayed ventricular relaxation.
7. Early diastolic filling rate decreases with age, but this buffered by an increase in late diastolic filling. This partly explains the correlation between increased age and left atrial size, itself increasing the likelihood of atrial fibrillation (AF).
8. A progressive decline in atrial pacemaker cells (>50%) leads to a decrease in intrinsic automaticity and increased risk of atrial arrhythmias.
9. Decreased stroke volume results in decreased cardiac output.
10. Both aortic arch and carotid sinus baroreceptor function is impaired (delayed) with attenuation of the heart rate response to changes in arterial pressure. This, combined with age-related autonomic dysfunction (see under Nervous System) compromises haemodynamic homeostasis. Blood pressure becomes more labile, with increased incidences of postural hypotension, post-prandial hypotension, sinus node depression, carotid sinus syndrome, and syncope. It is important to appreciate that the baroreceptor deterioration is multifactorial (reduced arteriolar compliance, blunted transduction of stretch signals, altered central neural processing, altered baseline efferent autonomic outflows, and damped end-organ responsiveness).
11. The heart rate response to exercise is attenuated. Despite this, regular aerobic exercise improves physiological functional capacity, VO_2 max, aerobic capacity, arterial compliance, and endothelium-dependent dilatation. Exercise also is helpful in raising free oxygen radical scavenging capacity, regenerating endothelium and intima-media wall thickness.
12. There is reduced compliance of the venous system, with decreased ability to buffer changes in volume.

Respiratory System

1. Loss of elasticity in the bony thorax and airways leads to easily collapsible alveoli, leading to a decreased surface area available for alveolar gas exchange.
2. The concomitant loss of muscle mass typical with ageing complicates the situation; muscles involved in respiration are weakened. There is increased chest wall rigidity. As a result, FRC is increased while total lung capacity remains unchanged.
3. Closing capacity (CC) encroaches on tidal volume resulting in V/Q mismatching and reduced PaO_2. CC reaches FRC by the mid-forties in the supine position, and by 66 when upright. Closure of lung bases redistributes inspired gas to apical areas of the lung which are underperfused (increasing dead space) while dependent areas of the lung are underventilated (increased shunt). Shunt tends to be the predominating factor.

4. The age related-effect on normal arterial oxygen tension may be estimated using the following formula:

    i. PaO_2 (kPa) = 13.3 – (age/30)

    ii. Aside from V/Q mismatching, the reduced PaO_2 reflects altered lung mechanics, diminished diffusion capacity, and reduced cardiac output resulting in increased oxygen extraction and reduced mixed venous oxygen tension.

5. Compliance across the lung is reduced in a non-uniform fashion: some regions still empty normally, while passive exhalation is slowed in others.
6. Lung expansion is less effective as respiratory rate increases, further exacerbating V/Q mismatching.
7. Centrally, there is a blunted CNS response to both hypoxia and hypercapnia

Nervous System

1. Neural density decreases: 30% of brain mass is lost by age 80, primarily grey matter.
2. A reduction in neurotransmitters (including catecholamines, serotonin, and acetylcholine) leads to subsequent deleterious effects on mood, memory and motor function.
3. Cortical binding sites for serotonin, GABA and catecholamines become depleted.
4. Signal transduction in the brainstem and spinal cord progressively declines.
5. There is loss of motor, sensory and autonomic fibres in the PNS, with reduction in both afferent and efferent conduction velocity
6. Axons innervate fewer muscle cells, leading to denervation and muscle atrophy.
7. The dominant autonomic tone gradually becomes sympathetic as baseline parasympathetic outflow decreases. Despite this, the response to beta-adrenergic stimulation is blunted.
8. Circadian rhythm alters as we age, typically leading to fewer hours of effective sleep, attenuated natural body temperature rhythms, and early awakening. Individuals may compensate by going to bed earlier. Cognition is typically best in the morning and worsens during the day.

Endocrine System

1. Alterations in signal transduction may decrease the ability of target organs to respond to target hormones.
2. Concentrations of many hormones change with age, but with little demonstrable clinical relevance.
3. A higher serum ADH concentration may result from altered baroreceptor function, placing the elderly at risk for hyponatraemia.
4. Carbohydrate intolerance increases through a variety of mechanisms (mainly increased adiposity, loss of muscle mass and decreased fitness).
5. Reduced Vitamin D synthesis in skin leads to decreased calcium absorption and predisposes to osteopenia and osteoporosis.
6. Menopause in females predisposes to osteoporosis. Testosterone secretion in males falls progressively after the mid-forties and may be significant, leading to the so-called partial androgen deficiency of the ageing male (PADAM).
7. Insulin resistance may reflect ageing and apoptosis of pancreatic islet beta-cells, predisposing to Type 2 Diabetes.

Renal Changes

1. Loss of renal mass begins from the fourth decade, and is predominantly cortical with relative sparing of the medulla.
2. The number of glomeruli is reduced. Sclerosis and diminished lobulation of existing glomeruli lead to reduced filtration areas and hence an age-related decline in GFR.
3. Tubular atrophy and fibrosis is common.

4. Even in the absence of diabetes, hypertension or chronic renal disease, glomerular basement membrane permeability increases, leading to some degree of microalbuminuria and proteinuria.
5. Renal blood flow declines progressively by 10% per decade after the age of 30, mainly in the cortex with a relative increase in flow to the juxtamedullary region.
6. Impaired vasodilatation of the afferent arteriole due to an imbalance of humoral factors.
7. Creatinine clearance is influenced by nutritional status, protein intake, muscle mass, body weight, gender, and ethnicity. As muscle mass generally decreases with ageing and urinary creatinine excretion decreases, the result is that the declining GFR is accompanied by lower rises is serum creatinine (relative to younger patients).

Immunological Changes

1. Senescence of immune cells predisposes to infection and delayed recovery.
2. Both innate and acquired immunity are affected.
3. Macrophage, B- and T-cell function decline, resulting in impaired humoral and cellular responses.
4. Dendritic cell number decreases, but function appears unimpaired.
5. Complement system activation is blunted in response to inflammation.
6. A reduced capacity to generate inflammatory mediators such as TNF-alpha, interleukin-1, and nitric oxide predispose to reactivation of dormant infections (e.g. shingles, TB) and susceptibility to new infections.
7. Increased autoimmunity occurs, with an increase in autoantibodies (both specific and non-specific.)

Gastrointestinal System

1. With age, there is desynchronization between the contraction and relaxation mechanisms in the oropharynx and oesophagus during swallowing.
2. Impaired taste and smell, faster antral filling and early satiation (the latter due to elevated cholecystokinin and reduced ghrelin levels) may predispose to age-related anorexia.
3. HCl and pepsin secretion are decreased, causing a small rise in gastric pH.
4. Calcium absorption is impaired, but it is not known whether this is due to vitamin D deficiency (common in the elderly) or a primary malabsorption process.
5. Prolonged gut transit time predisposes the elderly to constipation.

The Skin

1. Impaired barrier function, reduced epidermal cell turnover, and a reduction in keratinocyte and fibrinolytic result in increased fragility and loss of elasticity; this occurs in tandem with sunlight-induced photo-ageing which becomes more prominent over the years.
2. Reduced vascularity results in fibrosis and skin atrophy.
3. Parallel immune senescence renders skin more vulnerable to infection and neoplasia.

Musculoskeletal System

1. Sarcopenia (loss of muscle strength) reflects a 30% decline in muscle mass from the 3rd to the 8th decade with reduced cross-sectional area.
2. Mainly Type II (fast-twitch) muscle fibres are reduced, significantly reducing VO_2 max and force of contraction. Habitual aerobic exercise counteracts this. Slow-twitch fibres are relatively spared.
3. Loss of elasticity in joints (due to changes in collagen structure) is near universal.
4. Males over 50 lose bone at a rate of 1% per year, whereas loss is 2-3% in women after menopause. The loss in bone mineral density predisposes to osteopenia and osteoporosis with an increased risk of fractures.

Energy and Thermoregulatory Changes

1. Reduced total energy expenditure and physical activity may reduce basal metabolic rate (BMR) by as much as 20%.

2. Gluconeogenesis, fatty acid oxidation and Na^+/K^+/ATPase activity are all reduced with altered mitochondrial membrane permeability.
3. The threshold for detecting changes in skin temperature rises with ageing. Decreased vasomotor responses result in skin being less able to conserve or lose heat appropriately. Shivering threshold and shivering effectiveness are impaired. The net effect is that the elderly are at higher risk from adverse effects in both hot and cold environments (heat exhaustion/dehydration and hypothermia, respectively.)

References

1. Kaeberlein, M., 2007. Molecular basis of ageing: Meeting Report, *European Molecular Biology Organization Reports*, Vol 8(10)
2. Liu, J., 2014. Molecular mechanisms of ageing and related diseases. *Clin Exp Pharmacol Physiol* 41, 445-458
3. Maguire, S and Slater, B., 2013. Physiology of Ageing. *Anaesthesia and Intensive Care Medicine* 14(7)
4. Navaratnarajah A and Jackson, S., 2013. The physiology of ageing. *Medicine* 41(1)