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PHYSIOLOGY OF HUMAN AGEING

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SUMMARY

The study of human ageing physiology is limited by confounders such as concomitant disease, as well as the role of environmental factors and interactions with the physical world. The objective of this chapter is to review human physiological ageing through primarily a systems-based approach, with consideration for the geriatric syndromes (multifactorial pathophysiology), resiliency, and common ageing mechanisms that may underlie declines in multiple physiologic systems. Each system has its own trajectory for age-related dysfunction with accompanying system-specific declines. There are a growing number of examples of factors that regulate the resilient responses to stressors and mitigate potential adverse physiological consequences. Common mechanisms that contribute to human age-related physiology include chronic, low-grade, non-microbial inflammation, cellular senescence, accumulation of damaged macromolecules (DNA, proteins, carbohydrates, lipids), and stem and progenitor cell dysfunction. Ageing physiology in humans is heterogeneous and almost always interdependent with other systems and extrinsic influences.

INTRODUCTION

The study of human ageing physiology is confounded by chronic diseases not easily distinguished from primary ageing processes and for which ageing is the major risk factor. Nevertheless, and to the extent possible, ageing physiology will be reviewed as a systems-based approach, highlighting the major or key ageing features seen in healthy individuals. For many system-based ageing changes, the aetiologies are multifactorial or syndromic, and the geriatric syndromes such as pressure ulcers, incontinence, falls, dementia, and osteoporosis are good examples of the clinical consequences due predominately to ageing physiology in skin, the genitourinary system, muscle, central nervous system, and bone, respectively, but also secondary to contributions from physiologic ageing in other systems and extrinsic factors (e.g., polypharmacy, amount of daily activity, etc.).

Human ageing physiology is heterogeneous among individuals, lending itself to the descriptors of "normal" and "successful" ageing and supporting the concept of resiliency in the case of the latter. Resilience to physiologic ageing has been demonstrated across several systems, although its description in humans, outside of psychological and behavioural studies, is relatively limited (*Hadley* et al., 2017). Common mechanisms contribute to ageing physiology in animal models, and control of these mechanisms likely mediate resistance

effects. In humans, early evidence suggests that the same common ageing mechanisms are at play (*Kirkland*, 2016).

LIMITATIONS TO STUDYING HUMAN AGEING PHYSIOLOGY

Declines with age in physiological systems are commonly due to the effects of disease superimposed on fundamental ageing processes. A major challenge therefore is to distinguish the effects of ageing from disease. In humans, this can only be approximated by studying healthy individuals, tissue donors, those who experience non-disease related sudden death, or probably less helpful, autopsied individuals where the circumstances of death can be obtained. With this caveat, the physiology of system-specific human ageing is often considered to reflect primary process(es).

Superimposed on primary ageing processes, are environmental factors and interactions with the physical world that may regulate the degree and pace of these processes. For example, barrier facilities for animal models limit understanding of ageing processes influenced by the microbiome and immunological responses to environmental pathogens, which are applicable to animals in the wild and to humans. Behavioural factors, which rely on interactions with individuals, are also relevant since purposeful living, social networks and support systems influence health outcomes and mortality risk (*Boyle* et al., 2010a,b; *Holt-Lunstad* et al., 2010; *Park* et al., 2014).

Death is a poor endpoint to study ageing. Mortality is tightly linked to disease state and accidental death where ageing physiology is obscured by disease pathology and events unrelated to ageing, respectively. Furthermore, in the wild most animals will never achieve longevity close to their maximum life span because of death due to accidental reasons and to predation.

Finally, a specific physiological system may be dependent on multi-system interactions, and so dysfunction in one system may be related to dysfunctional processes in another or multiple systems. This relationship is true in disease states such as cardiopulmonary, cardiorenal, and hepatorenal syndromes, where dysfunction due to disease in one system contributes to the progression of disease in another system. The geriatric syndromes represent the equivalent dysfunctional outcomes due to ageing in one system being influenced by ageing in other systems and/or multiple age-related aetiologies that may be intrinsic or extrinsic to the individual. Therefore, examination of age-related changes in a single physiological system in isolation is confounded by the contributions of ageing in interacting systems.

DISRUPTION OF PHYSIOLOGIC RHYTHMS WITH AGEING

With ageing, disruption of circadian patterns cause phase advances (1-2 hours earlier) such as in the 24-hour body temperature trough and sleep onset. Suprachiasmatic nucleus neuronal loss in the hypothalamus results in attenuated pulsatile secretions and decreases in gonadotropins, growth hormone (GH), thyrotropin, melatonin, and adrenocorticotropic hormone (ACTH) (*Veldhuis*, 1997). There is also a delayed reset to a new photoperiod with ageing (*Hofman* and *Swaab*, 2006).

AGE-RELATED CHANGES IN THE GASTROINTESTINAL SYSTEM

Oropharynx

With ageing, there is a decrease in acinar cells and saliva production that is accompanied by thinning of the oral mucosa (*Smith* et al., 2013). These changes contribute to dry mouth complaints, recession of gums over time, and the increased risk of root carries. Loss of teeth promotes less effective mastication. Abnormal transfer of the food bolus to the pharynx (due to decreased oesophageal muscle compliance) is a major cause of inadequate nutritional intake in edentate individuals and places them at increased aspiration risk (*Fulp* et al., 1990; *Frederick* et al., 1996).

Oesophagus

There are four pathophysiological processes that occur in the oesophagus during ageing, including hypertrophy, nerve loss, decreased contraction/tone, and decreased sensation. Skeletal muscle hypertrophy of the upper one-third of the oesophagus carries no functional consequences (*Hall* et al., 2005). There is loss of myenteric ganglion cells which cause a decline in the amplitude of oesophageal contractions during peristalsis, but this does not substantially cause impairment of food movement (*Hall* et al., 2005). However, major deficits in secondary oesophageal contractions and a decrease in lower oesophageal sphincter tone causes increased gastric acid exposure (*Kekki* et al., 1982; *Feldman* et al., 1996; *Hurwitz* et al., 1997; *Haruma* et al., 2000,). Impaired sensation of distension at the distal oesophagus contributes to loss of symptomatology from injury (*Lasch* et al., 1997).

Stomach

Acidification of gastric contents with ageing is intact in the basal unstimulated state; however, there is an increased prevalence of *H. pylori* infection (*Marshall*, 1994; *Haruma* et al., 2000). Higher rates of gastritis, decreased production of prostaglandins, bicarbonate, and non-parietal fluid in the setting of decreased gastric emptying and microcirculation lead to impaired mucosal defences (*Guslandi* et al., 1999; *Tarnawski* et al., 2014). There is also a greater susceptibility to injury, with impaired healing and reduced efficacy of ulcer-healing drugs (*Tarnawski* et al., 2014).

Small intestine

Moderate villus atrophy and decreased absorption of micronutrients (e.g., calcium, folic acid, vitamin B12) with ageing are accompanied by an increase in bacterial overgrowth (*Parlesak* et al., 2003; *Salles*, 2007). Loss of innervation, especially of sensory and myenteric nerves, result in a higher incidence of painless ulcers (*Hilton* et al., 2001).

Large intestine

Mucosal atrophy, atrophy of the muscularis externus and altered coordination of contraction contribute to decreased colonic motility and the much higher rates of constipation with ageing (*Bitar* and *Patil*, 2004). Loss of myenteric plexus and intrinsic sensory neurons and concomitant lower anal sphincter tone lead to faecal incontinence (*Wade* and *Hornby*, 2005). Hypertrophy of muscularis mucosa with atrophy of the muscularis externus predispose to diverticuli (*Comparato* et al., 2007; *Commane* et al., 2009). Barrier function of colonic epithelium is compromised with ageing (*Tran* and *Greenwood-Van Meerveld*, 2013).

Hepatobiliary system

Liver mass and perfusion decline with ageing (*Schmucker*, 2005). There is

impairment in synthetic function, with a slight decrease in albumen levels, lower LDL and LDL receptor levels, lower cytochrome P450 content and lower vitamin K-dependent clotting factors (*Sotaniemi* et al., 1997; *Fu* and *Nair*, 1998; *Schmucker*, 2005). The regenerative response to injury decreases and the bile lithogenic index increases with ageing (*Valdivieso* et al., 1978; *Schmucker*, 2005).

Exocrine pancreas

There are minor atrophic fibrotic changes in the ageing pancreas with an increased number of cysts and side branching of ducts (*Bulow* et al., 2014). Although there is a decline in stimulated pancreatic flow, this does not impact exocrine function.

CARDIOVASCULAR AGEING

Heart weight increases as a function of ageing, with enlargement of the left atrium and enlargement and hypertrophy of the left ventricle (*Kitzman* et al., 1988). A decrease in cardiomyocyte number is accompanied by an increase in cardiomyocyte size (*Olivetti* et al., 1991). The aortic valve and mitral annulus thickens with development of calcific deposits. Mitral annular calcification predisposes to conduction abnormalities. Increased atrial and ventricular premature beats become more common with age (*Fleg* and *Kennedy*, 1992).

Due mostly through compensatory mechanisms, ejection fraction, stroke volume, and cardiac output do not change substantially with ageing (*Ferrari* et al., 2003). There is an increase in early diastolic filling, and an increase in end-diastolic filling due to a compensatory greater contribution from atrial systole (marked by a normal S4 in older individuals). There is a relative loss of chronotropic and inotropic responsiveness to β-adrenergic stimuli/catecholamines as well as inotropic response to digitalis glycosides. Peak cardiac output to maximal exercise is decreased.

In the vasculature, arterial wall thickness (intima-media) increases with advancing age, as does pulse wave velocity and total peripheral resistance (*Mitchell*, 2008). Endothelial nitric oxide release and β-adrenergic-mediated vasodilation decreases (*Mitchell*, 2008).

AGEING OF THE RESPIRATORY SYSTEM

Three hallmark features describe ageing in the respiratory system: change in lung volumes, increased alveolar-arterial oxygen gradient, and ventilation-perfusion mismatch (*Chan* and *Welsh*, 1998). Due to decreased elastic recoil, increased chest wall rigidity, and a loss of force-generating capacity of respiratory muscles, forced vital capacity, forced expiratory volume at 1 second, and vital capacity decrease and functional residual capacity increases (*Janssens*, 2005). Diminished lung diffusion capacity results in an increase in the alveolar-arterial oxygen gradient, measured as the diffusion capacity of carbon monoxide which drops by 2-3 ml/min/mmHg per decade (*Stam* et al., 1994). Secondary to decreased elastic recoil, the intrapleural pressure becomes less negative causing areas of the lung base to close. With this closure, there is a redistribution of inspired air to underperfused apical areas. The resultant increase in physiological dead space and underventilation of

dependent lung areas is responsible for ventilation-perfusion mismatches typical of the ageing lung (*Stam* et al., 1994).

AGEING OF THE IMMUNE SYSTEM

Ageing of the immune system is reflected by diminished immune responsiveness, so-called "immunosenescence", altered immune system physiology, and impaired immune regulation. Due to immunosenescence (*Agarwal* and *Busse*, 2010), there is a decreased response to new antigens/elevated susceptibility to infection and cancer, decreased vaccine efficiency (e.g., influenza), reactivation of latent infections (e.g., herpes simplex virus, tuberculosis), and perhaps compromised immune surveillance.

Important changes in immune system physiology with ageing include decreased production and maturation of B- and T-cells (e.g., marrow decline, thymic involution), inversion in proportional representation of memory vs naïve cells (T memory cells increase and T naïve cells decrease with age), decreased isotype switching and affinity maturation of B cells, accumulation of CD28-negative T-cells, and impaired formation of the T-cell – Antigen Presenting Cell "immune synapse" (*Panda* et al., 2009).

Altered immunoregulation can be seen as an increase in autoimmune syndromes (systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis, others), oligoclonal expansion of T- and B-cells (decrease in diversity with age), monoclonal gammopathies, and increased inflammation (*Ramos-Casals* et al., 2004; *Arai* et al., 2015; *Ray* and *Yung*, 2018).

CHANGES IN THE AGEING KIDNEY

Kidney weight and volume remain unchanged with ageing in individuals who experienced sudden death and in healthy individuals, respectively (*Glassock* and *Rule*, 2012). Nephrosclerosis increases progressively with age (*Glassock* and *Rule*, 2012). A sclerosis score is the total number of histological abnormalities (global glomerular sclerosis, any tubular atrophy, interstitial fibrosis > 5%, any arteriosclerosis). Among living kidney donors with less than 10% glomerulosclerosis, glomerular density declines with age but the size of glomeruli and tubules increase; in those with greater than 10% glomerulosclerosis, glomerular density increases with age with a rise in the number of small sclerotic glomeruli and tubular atrophy. The number of functional glomeruli decreases with age in both live kidney donors and in individuals at autopsy. There is compensation by functional nephrons in older healthy individuals. Glomerular filtration rate (GFR) is mostly reported to decline with age, but is variable and may be unchanged in as much as one-third in healthy cohorts (*Lindeman* et al., 1985; *Esposito* et al., 2007). Estimated GFR tends to vary based on the formula employed, and can be underestimated in healthy older adults when age is used as a surrogate for muscle mass. Changes in renal function with age may in part be driven by a vascular process whereby vasoconstrictive responses to angiotensin are intact but the vasodilatory responses to acetylcholine or to an acute sodium load are impaired (*Hollenberg* et al., 1974).

Table 1: Changes in the haematopoietic system with age

Parameter	Change with age	Response to challenges with age
Red cell life span	=	
Iron turnover	=	
Blood volume	=	
Bone marrow mass/cellularity	↓	
Bone marrow fat	↑	
Donor suitability for haematpoietic cell transplantation	↓	
Tolerance of chemotherapy	↓	↓
Compenstory response to:		
Phlebotomy		↓
Hypoxia		↓
Colony size of stimulated erythroid progenitor cells		↓
Production of BM stimulatory hormones (e.g. SCF, GM-CSF, IL-3)*	↓	↓
Total WBC	=	
Clonal expansion of specific white blood cells	↑	
Platelets (total number)	=	
Platelet responsiveness	↑	
Bleeding time	↓	↓
Procoagulant state (↑fibrinogen, ↑Factors V, VII, VIII, IX, ↑kininogen, ↑prekalikrein	↑	↑
Fibrin degradation products (D-dimers)	↑	
Plasminogen activator inhibitor-1 (major inhibitor of fibrinolysis)	↑	
Deep vein thrombosis	↑	↑

↑: Increase; ↓: Decrease; =: Unchanged.
*SCF: Stem cell factor; GM-CGF: Granulocyte-Macrophage-Colony-stimulating factor; IL-3: Interleukin-3.

AGEING IN THE HAEMATOPOIETIC SYSTEM

Changes in the haematopoietic system with age are shown in Table 1. Major changes outside of the immune system (see above) include decreased bone marrow, marrow cellularity, and compensatory responses to phlebotomy and hypoxia as well as increased components related to the procoagulant state

Table 2: Endocrine changes with ageing

Hormone	Change with ageing
Growth hormone	N in males; ↓ in females
Insulin-like growth factor I	↓
ACTH	N
Cortisol	N
DHEA	↓
Renin	N
Aldosterone	↓
TSH	N or ↑
T_4	N
T_3	↓
PTH	↑
Calcitonin	↓
1,25 $(OH)_2$ D	↓
LH	↑ or N in males; ↑ in females
FSH	↑ or N in males; ↑ in females
Testosterone	↓ or N in males; ↑ in females
Free testosterone	↓
Atrial natriuretic factor	↑
Insulin	↑
Glucagon	↓

↑: Increase; ↓: Decrease; N: Normal.
DHEA: dehydroepiandrosterone; TSH: thyroid stimulating hormone; T: thyroxine;
PTH: parathyroid hormone; LH: luteinizing hormone; FSH: follicle stimulating hormone.

(*Lipschitz* et al., 1984; *Pinto* et al., 2003; *Franchini*, 2006). In a young adult, haematopoietic marrow (red) resides in skull, vertebra, flat bones, and proximal femoral and humeral metaphyses. Fatty marrow (yellow) predominates in remainder of skeleton, and gradually replaces red marrow with age (*Custer* and *Ahlfeldt*, 1932; *Kricun*, 1985).

ENDOCRINE CHANGES WITH AGEING

Table 2 summarizes the endocrine changes with ageing (*Lamberts* et al., 1997). In healthy individuals, levels of some hormones are not altered with age (e.g., thyroid hormone). In older individuals without disease, the homeostatic setpoint for a given hormone may be the same as in youth, at expense of alteration in another (e.g., "normal" testosterone with elevated LH), different from youth (e.g., DHEA, IGF-1 levels decline with age) or the same as in youth, except with a stressor (e.g., cortisol response).

There is an increase in frequency of endocrine disease with ageing (e.g., hypothyroidism, post-menopausal osteoporosis) and often older individuals have different presentations of endocrine disease (e.g., hypothyroidism, hyperthyroidism) (*Gambert* and *Escher*, 1988). Different presentations

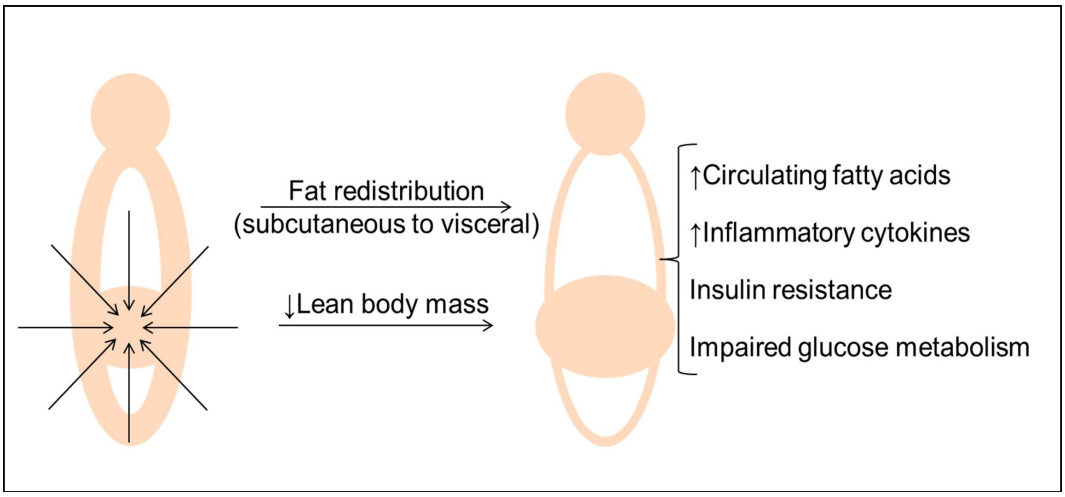

Figure 1: Changes in adipose tissue with ageing.

of non-endocrine disease are also common when coexistent with endocrine disease (e.g., angina in the setting of hyperthyroidism). In addition, there are alterations in hormones secondary to medications frequently prescribed in the elderly (e.g., hyperprolactinemia from phenothiazines).

Although not as abrupt as the decline in oestrogen levels during menopause, there are inexorable declines in testosterone ("andropause"), DHEA ("adrenopause"), and GH/IGF-I ("somatopause"). These changes, mediated by declines in LH/FSH, ACTH, and GH, respectively, are controlled at the level of the hypothalamus-pituitary complex (*Jones* and *Boelaert*, 2015).

AGE-RELATED CHANGES IN ADIPOSE TISSUE

Two major changes in adipose tissue that occur with ageing are the re-distribution of fat and the decrease in lean body mass (Figure 1). Adipose tissue redistributes from subcutaneous to visceral depots (*Kuk* et al., 2009). This redistribution is accompanied by an increase in circulating fatty acids and inflammatory cytokines as well as insulin resistance and impaired glucose metabolism (*Stout* et al., 2017). When older individuals are compared to younger ones, even after controlling for waist circumference, visceral fat increases and subcutaneous fat decreases (*Kuk* et al., 2009).

MUSCLE AGEING

The hallmark of muscle aging, sarcopenia, is operationally defined by thresholds of muscle loss, decreased muscle strength, and lower physical performance (*Locquet* et al., 2018). Risk of sarcopenia is very well predicted by the combination of age, grip strength, and calf circumference (*Locquet* et al., 2018). Loss of muscle mass as a proportion of body weight is almost universal with ageing and muscle loss in the lower extremities is greater than

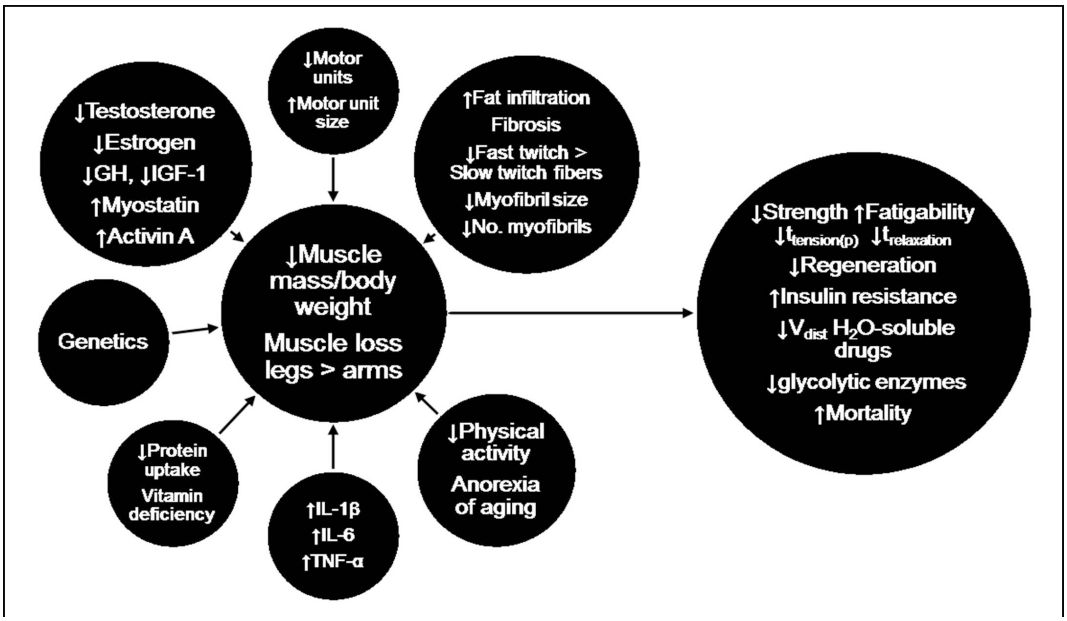

Figure 2: Contributing factors to muscle ageing (left) and consequences of sarcopenia (right).

that in the upper extremities. The loss of muscle mass is attributed to the decrease in motor unit number and size, lower physical activity common in older individuals, elevated inflammatory cytokines, diminished testosterone, oestrogen, and GH/IGF-I levels, elevations in myostatin and activin A, as well as nutritional deficits and genetic predisposition (Figure 2) (*Narici* and *Maffulli*, 2010). Histomorphologically, aged muscle shows increased fatty infiltration, fibrosis, decreased fast twitch > slow twitch fibers, smaller myofibril size, and fewer myofibrils (*Faulkner* et al., 2007).

Functional and clinical consequences of muscle ageing include decreased strength, increased fatigability, shorter time to peak tension and time to relaxation, decreased regenerative capacity, greater insulin resistance, lower volume of distribution for water-soluble drugs and decreased levels of glycolytic enzymes (*Narici* and *Maffulli*, 2010). Increased mortality is associated with sarcopenia (*Reinders* et al., 2015).

SKIN AGEING

Primary changes that occur with skin ageing include epidermal thinning, decreased vascularity, and the loss of rete pegs which project downward from the epidermis between the dermal papillae (*Montagna* and *Carlisle*, 1990). The elastin network of the skin is diminished, there is a loss of subcutaneous fat, and epidermal turnover is slowed (*Uitto*, 2008). Histologically, there is a loss of melanocytes, Langerhans' cells, sweat and sebaceous glands, as well as Meissner's and Pacinian corpuscles (*Yaar* and *Gilchrest*, 2001). Microarchitectural changes lead to poor nutrient transfer, a loss of protective lipids, and decreased area for heat transfer. Bleeding can more easily occur into dermal-epidermal space. Clinically, the ageing skin demonstrates an

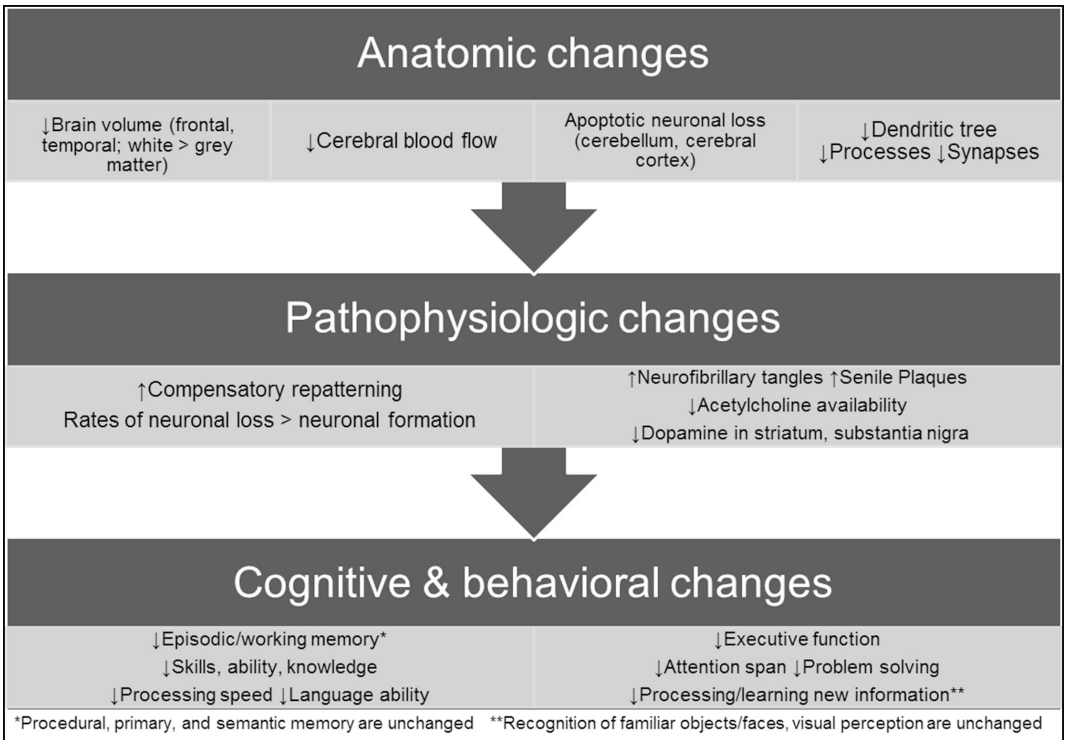

Figure 3: Ageing in the central nervous system by major anatomic, pathophysiologic, as well as cognitive and behavioural changes.

increased fragility to shear stress, slower wound healing, xerosis, reduced barrier function, compromised thermoregulation, wrinkling and sagging, decreased sensory perception, and purpura.

CENTRAL NERVOUS SYSTEM (CNS) AGEING

Key features of ageing in the CNS are outlined in Figure 3. Anatomically, the brain volume decreases, with predominant losses in the frontal and temporal lobes and with greater loss of white versus grey matter. Cerebral blood flow declines. Apoptotic neuronal loss becomes prominent in the cerebellum and cerebral cortex (*Dorszewska*, 2013). There is a reduction of the dendritic tree, loss of neuronal processes, and diminution of synapses (*van der Zee*, 2015).

Despite compensatory repatterning due to neuronal loss, the rate of neuronal loss exceeds that of neuronal formation. Pathological findings such as increased neurofibrillary tangles and senile plaques become more evident, although are not present to the extent that would be found in Alzheimer's disease (*Fjell* et al., 2014). There is reduced acetylcholine availability due to loss of cholinergic and muscarinic neurons, as well as lower synthesis and release of acetylcholine. Diminished levels of dopamine are found in the striatum and substantia nigra (*Klostermann* et al., 2012).

Cognitively, episodic and working memory declines (*Wilson* et al., 2002). There is a loss of specific skills and

knowledge with reduced processing speed and language ability. Executive function declines, as doses attention span, problem solving, as well as processing and learning new information. Procedural, primary, and semantic memories are unchanged with age. Recognition of familiar objects and faces and visual perception remain unaffected in healthy older adults.

SENSORY CHANGES WITH AGE

Vision

Periorbital tissues atrophy and lacrimal gland function, tear production, and goblet cell function are reduced with ageing (*Van Haeringen*, 1997). Despite decreased tear production, watery eyes are a common phenomenon since tissue atrophy leads to less effective drainage.

With ageing, the lens increases in thickness and hardness and the ciliary muscle decreases in strength; together, presbyopia or farsightedness results (*Strenk* et al., 2005). The lens also yellows and becomes more opaque with age, lessening colour discrimination. Increased light scatter due to lens alterations also reduces contrast. The resting pupil size and responsiveness decreases. In older individuals, the cornea yellows, undergoes focal and generalized thickening, and is more likely to have Hasall-Henle warts and especially arcus senilis (*Salvi* et al., 2006). There is a decrease in the production and drainage of the aqueous humour in the ageing eye, reduced speed and accuracy of pursuit and saccadic eye movements, and accumulation of scleral calcifications (Cogan's plaques) (*Salvi* et al., 2006) . There is a loss of retinal pigment epithelial cells which contributes to the decreases in number, size, and function of rods in the retina (*Liem* et al., 1991). Although the number of cones in the fovea is unchanged with age, their function is reduced. Vitreous floaters due to collagen condensations increase with age. Blood flow to the visual cortex is decreased.

Hearing

In the ageing ear, there is a loss of hair cells in the organ of Corti, decreased innervation of cochlear and auditory centres in the brain, stiffness and calcification of the basilar membrane of the sensory apparatus, thickening of the stria vascularis capillaries (source of endolymph), and degeneration of the spiral ligament (*Howarth* and *Shone*, 2006). Hearing loss due to these changes are usually of high frequency sound (presbycusis) and result in reduced speech discrimination, poor localization of the sound source, and decreased ability to discriminate between target sound and background noise (*Howarth* and *Shone*, 2006).

Taste and smell

There is a reduction in papillae on tongue and decreased taste sensitivity with ageing. Uneven gustatory deficiencies across the tongue exist, but the loss of taste in older individuals is due mostly to an impaired sense of olfaction (*Boyce* and *Shone*, 2006).

Detection thresholds for smelling are altered with age owing in part to a decrease in the number of sensing neurons (*Boyce* and *Shone*, 2006). This results in an underappreciated reduction in appetite, the extremes of which can be best appreciated in the observation that people with anosmia forget to eat.

AGEING OF THE GENITOURINARY SYSTEM

Bladder

Decreased innervation of the detrusor muscle and CNS changes lead to diminished detrusor contractility, lower maximum bladder capacity and flow rate, reduced ability to withhold voiding, and an increased post-void residual volume (*Elbadawi* et al., 1998). The constellation of these age-related alterations greatly increases the risk for urinary incontinence. The decline in oestrogen in women leads to a shorter urethral length, a reduced maximum urethral closure pressure, and less effective urethral barrier function (*Capobianco* et al., 2012); together, these factors predispose women to an increased risk of urinary tract infection.

Male reproductive system

Age-related neurologic, vascular, and endocrine changes in men lead to the greater stimulation required for erection, decreased spontaneous erections, diminished firmness of erections, lower force of ejaculation, smaller ejaculate volumes, and increased refractory times between erections (*Seftel*, 2005). Despite these changes, reports of lower sexual activity in older men are variable (*Lindau* and *Gavrilova*, 2010). However, an objective decline in male reproductive ability with advanced age is likely due to lower Leydig cell number, degeneration of the seminiferous tubules leading to diminished sperm production, an increase in sperm chromosomal abnormalities, reduced sperm motility, and a reduced ability of sperm to fertilize eggs (*Harris* et al., 2011). Enlargement of the prostate gland with ageing is common.

Female reproductive system

The loss of oocytes and ovarian dysfunction in older women is primarily responsible for the decline in oestrogen during the perimenopausal period and the reduction in implantation efficiency, decreased likelihood for pregnancy, lower number of live births, and poor success of *in vitro* fertilization (*Tarlatzis* and *Zepiridis*, 2003). Oestrogen deficiency causes diminished vaginal elasticity, reduced clitoral engorgement after stimulation, increased vaginal dryness and atrophy, as well as decreased cervicovaginal secretions (*Kingsberg*, 2002). Oestrogen deficiency is responsible for an increase in vaginal pH, which predisposes to colonization by enteric flora.

SYNDROMIC APPROACH

For many if not all system-specific ageing changes, multiple aetiologies are at play, including the influence of ageing changes in other physiologic systems. While characterizing ageing in a single system *in isolation* serves to simplify the task, it also minimizes the true nature of its complex regulation. The geriatric syndromes serve as examples of the complexity involved to fully explain common age-related changes. Geriatric syndromes have been operationally defined as multi-factorial, having multi-system involvement, and sharing risk factors such as older age, functional impairment, and impaired mobility (*Inouye* et al., 2007). Common geriatric syndromes include pressure ulcers, incontinence, falls, delirium, dementia, and osteoporosis.

Osteoporosis is the hallmark of bone ageing (*Chandra* et al., 2018) and will be used here as an illustration of the syndromic approach to describing physiologic ageing in the skeleton (Figure 4). Bone loss is ultimately the

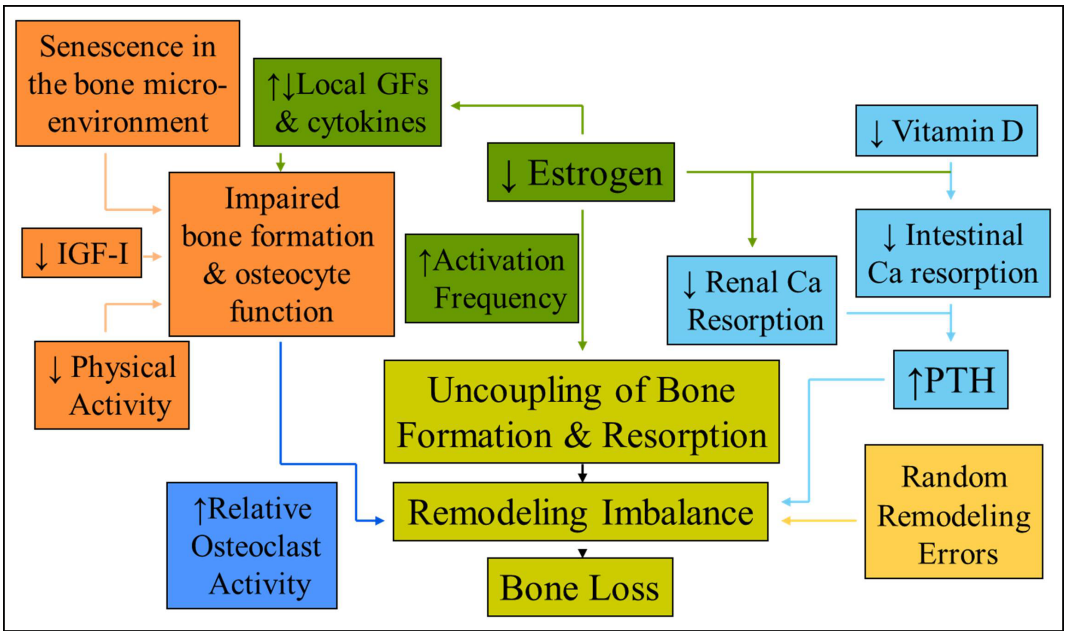

Figure 4: Osteoporosis as an example of a geriatric syndrome with multifactorial aetiologies for bone ageing.

result of a remodelling imbalance, where an uncoupling of bone formation to bone resorption causes a net loss of bone tissue. There are at least three major contributions to age-related bone loss: secondary hyperparathyroidism due to vitamin D deficiency and decreased renal calcium absorption, impaired bone formation and osteocyte function and, in both women and men, lower oestrogen levels.

Cell senescence in the bone micro-environment, declines in IGF-I levels, and decreased physical activity and response to mechanical loading contribute to poor bone formation. In the setting of unimpaired osteoclast function, there is a relative increase in bone resorption. With the decline in oestrogen, two key phenomena occur which contributes to bone loss; there is an increase in the activation frequency of osteoclasts (i.e., initiation of local resorption events) and there are alterations in local growth factors and cytokines favouring an inflammatory milieu with inhibitory effects on bone formation. There are also random remodelling errors that may increase with ageing.

RESILIENCE TO PHYSIOLOGIC AGEING

It is well established that psychosocial factors influence resilience to age-related social and behavioural stressors, but there is a limited understanding of human resilience in responses to physiologic or pathologic stressors (*Hadley* et al., 2017). It is clear, however, that low levels of resilience confer vulnerability to stressors (Figure 5). Specific physiologic resilient responses differ depending on both the stressor being exerted and the clinical or physiologic property to be maintained or restored.

There are growing examples of

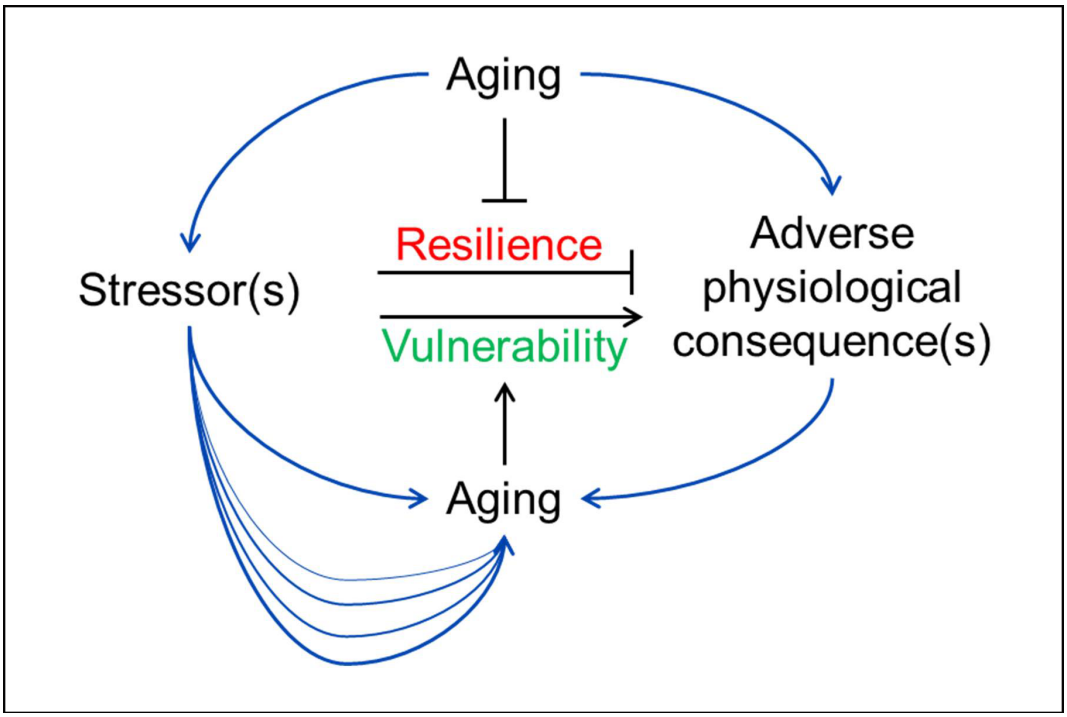

Figure 5: Relationships among stressors, aging, and resilience to adverse physiologic consequences.

resilient responses that are mediated by regulatory factors, which mitigate potential adverse consequences. Falls are common stressors in older individuals and can result in fractures, especially of the hip or wrist. Bone mineral density remains a very strong predictor of hip fracture up to 25 years after the measurement and preservation of femoral neck bone mass, even in individuals greater than age 75, does occur and minimizes the likelihood of fracture (*Black* et al., 2018).

Neuropathologic changes of Alzheimer disease (AD) uncommonly exist in isolation in the brains of older individuals, but are more often variably combined, or comorbid, with other lesions that underlie the dementia syndrome including vascular brain injury (VBI), Lewy body disease (LBD), and hippocampal sclerosis (HS). The frequency and severity of these neuropathologic changes in cognitively intact older individuals varies, with some showing a lesion burden considered sufficient evidence for dementia, a situation commonly referred to as apparent cognitive resilience. Here resilience to neuropathological stressors appears to be dependent on the presence of HS only, since cognitively intact individuals can have evidence for high lesion burden consistent with AD, VBI, and/or LBD at brain autopsy (*Latimer* et al., 2017).

COMMON MECHANISTIC APPROACH

There are common mechanisms thought to underlie physiologic ageing based on evidence in lower animal models which are now being confirmed

in non-human primates and in humans. These include chronic, low-grade, non-microbial inflammation, cellular senescence, accumulation of damaged macromolecules (DNA, proteins, carbohydrates, lipids), as well as stem and progenitor cell dysfunction (*Kirkland*, 2016).

In animal studies, targeting senescent cells using genetic or pharmacological approaches delays, prevents, or alleviates multiple age-related phenotypes associated with chronic diseases, geriatric syndromes, and loss of physiological resilience. In preclinical studies, reduction of senescent cell burden has successfully ameliorated frailty, cardiac dysfunction, vascular hyporeactivity and calcification, diabetes mellitus, liver steatosis, osteoporosis, vertebral disk degeneration, pulmonary fibrosis, and radiation-induced damage. Senolytic agents are being tested in proof-of-concept clinical trials based on these findings (*Kirkland* et al., 2017).

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LITERATURE

Agarwal, S. and Busse, P.J.: Innate and adaptive immunosenescence. Ann. Allergy Asthma Immunol. 104, 183-190; quiz 190-182 (2010).

Arai, Y., Martin-Ruiz, C.M., Takayama, M., Abe, Y., Takebayashi, T., Koyasu, S., Suematsu, M., Hirose, N., and von Zglinicki, T.: Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians. EBioMedicine 2, 1549-1558 (2015).

Bitar, K.N. and Patil, S.B.: Aging and gastrointestinal smooth muscle. Mech. Ageing Dev. 125, 907-910 (2004).

Black, D.M., Cauley, J.A., Wagman, R., Ensrud, K., Fink, H.A., Hillier, T.A., Lui, L.Y., Cummings, S.R., Schousboe, J.T., and Napoli, N.: The Ability of a Single BMD and Fracture History Assessment to Predict Fracture Over 25 Years in Postmenopausal Women: The Study of Osteoporotic Fractures. J. Bone Miner. Re.s 33, 389-395 (2018).

Boyce, J.M. and Shone, G.R.: Effects of ageing on smell and taste. Postgrad. Med. J. 82, 239-241 (2006).

Boyle, P.A., Buchman, A.S., Barnes, L.L., and Bennett, D.A.: Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. Arch. Gen. Psychiatry 67, 304-310 (2010a).

Boyle, P.A., Buchman, A.S., and Bennett, D.A.: Purpose in life is associated with a reduced risk of incident disability among community-dwelling older persons. Am. J. Geriatr. Psychiatry 18, 1093-1102 (2010b).

Bulow, R., Simon, P., Thiel, R., Thamm, P., Messner, P., Lerch, M.M., Mayerle, J., Volzke, H., Hosten, N., and Kuhn, J.P.: Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population. Eur. Radiol. 24, 3142-3149 (2014).

Capobianco, G., Donolo, E., Borghero, G., Dessole, F., Cherchi, P.L., and Dessole, S.: Effects of intravaginal estriol and pelvic floor rehabilitation on urogenital aging in postmenopausal women. Arch. Gynecol. Obstet. 285, 397-403 (2012).

Chan, E.D. and Welsh, C.H.: Geriatric respira-

tory medicine. Chest 114, 1704-1733 (1998).

Chandra, A., Rosenzweig, A., and Pignolo, R.J.: Osteobiology of Aging. In: Fractures in the Elderly (Eds.: Pignolo, R.J., Forciea, M.A., and Johnson, J.C.). 2nd Edition. Humana-Springer, New York, 3-37 (2018).

Commane, D.M., Arasaradnam, R.P., Mills, S., Mathers, J.C., and Bradburn, M.: Diet, ageing and genetic factors in the pathogenesis of diverticular disease. World J. Gastroenterol. 15, 2479-2488 (2009).

Comparato, G., Pilotto, A., Franze, A., Franceschi, M., and Di Mario, F.: Diverticular disease in the elderly. Dig. Dis. 25, 151-159 (2007).

Custer, R.P. and Ahlfeldt, F.E.: Studies on the structure and function of bone marrow. Part II. J. Lab. Clin. Med. 17, 960-962 (1932).

Dorszewska, J.: Cell biology of normal brain aging: synaptic plasticity-cell death. Aging Clin. Exp. Res. 25, 25-34 (2013).

Elbadawi, A., Diokno, A.C., and Millard, R.J.: The aging bladder: morphology and urodynamics. World J. Urol. 16, Suppl. 1, S10-34 (1998).

Esposito, C., Plati, A., Mazzullo, T., Fasoli, G., De Mauri, A., Grosjean, F., Mangione, F., Castoldi, F., Serpieri, N., Cornacchia, F., and Dal Canton, A.: Renal function and functional reserve in healthy elderly individuals. J. Nephrol. 20, 617-625 (2007).

Faulkner, J.A., Larkin, L.M., Claflin, D.R., and Brooks, S.V.: Age-related changes in the structure and function of skeletal muscles. Clin. Exp. Pharmacol. Physiol. 34, 1091-1096 (2007).

Feldman, M., Cryer, B., McArthur, K.E., Huet, B.A., and Lee, E.: Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. Gastroenterology 110, 1043-1052 (1996).

Ferrari, A.U., Radaelli, A., and Centola, M.: Invited review: aging and the cardiovascular system. J. Appl. Physiol. (1985) 95, 2591-2597 (2003).

Fjell, A.M., McEvoy, L., Holland, D., Dale, A.M., Walhovd, K.B., and Alzheimer's Disease Neuroimaging Initiative: What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog. Neurobiol. 117, 20-40 (2014).

Fleg, J.L. and Kennedy, H.L.: Long-term prognostic significance of ambulatory electrocardiographic findings in apparently healthy subjects greater than or equal to 60 years of age. Am. J. Cardiol. 70, 748-751 (1992).

Franchini, M.: Hemostasis and aging. Crit. Rev. Oncol. Hematol. 60, 144-151 (2006).

Frederick, M.G., Ott, D.J., Grishaw, E.K., Gelfand, D.W., and Chen, M.Y.: Functional abnormalities of the pharynx: a prospective analysis of radiographic abnormalities relative to age and symptoms. AJR Am. J. Roentgenol. 166, 353-357 (1996).

Fu, A. and Nair, K.S.: Age effect on fibrinogen and albumin synthesis in humans. Am. J. Physiol. 275, E1023-1030 (1998).

Fulp, S.R., Dalton, C.B., Castell, J.A., and Castell, D.O.: Aging-related alterations in human upper esophageal sphincter function. Am. J. Gastroenterol. 85, 1569-1572 (1990).

Gambert, S.R., and Escher, J.E.: Atypical presentation of endocrine disorders in the elderly. Geriatrics 43, 69-71, 76-78 (1988).

Glassock, R.J., and Rule, A.D.: The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. Kidney Int. 82, 270-277 (2012).

Guslandi, M., Pellegrini, A., and Sorghi, M.: Gastric mucosal defences in the elderly. Gerontology 45, 206-208 (1999).

Hadley, E.C., Kuchel, G.A., Newman, A.B., Workshop, S., and Participants. Report: NIA Workshop on Measures of Physiologic Resiliencies in Human Aging. J. Gerontol. A Biol. Sci. Med. Sci. 72, 980-990 (2017).

Hall, K.E., Proctor, D.D., Fisher, L., and Rose, S.: American gastroenterological association future trends committee report: effects of aging of the population on gastroenterology practice, education, and research. Gastroenterology 129, 1305-1338 (2005).

Harris, I.D., Fronczak, C., Roth, L., and Meacham, R.B.: Fertility and the aging

male. Rev. Urol. 13, e184-190 (2011).
Haruma, K., Kamada, T., Kawaguchi, H., Okamoto, S., Yoshihara, M., Sumii, K., Inoue, M., Kishimoto, S., Kajiyama, G., and Miyoshi, A.: Effect of age and Helicobacter pylori infection on gastric acid secretion. J. Gastroenterol. Hepatol. 15, 277-283 (2000).
Hilton, D., Iman, N., Burke, G.J., Moore, A., O'Mara, G., Signorini, D., Lyons, D., Banerjee, A.K., and Clinch, D.: Absence of abdominal pain in older persons with endoscopic ulcers: a prospective study. Am. J. Gastroenterol. 96, 380-384 (2001).
Hofman, M.A., and Swaab, D.F.: Living by the clock: the circadian pacemaker in older people. Ageing Res. Rev. 5, 33-51 (2006).
Hollenberg, N.K., Adams, D.F., Solomon, H.S., Rashid, A., Abrams, H.L., and Merrill, J.P.: Senescence and the renal vasculature in normal man. Circ. Res. 34, 309-316 (1974).
Holt-Lunstad, J., Smith, T.B., and Layton, J.B.: Social relationships and mortality risk: a meta-analytic review. PLoS Med 7, e1000316 (2010).
Howarth, A. and Shone, G.R.: Ageing and the auditory system. Postgrad. Med. J. 82, 166-171 (2006).
Hurwitz, A., Brady, D.A., Schaal, S.E., Samloff, I.M., Dedon, J., and Ruhl, C.E.: Gastric acidity in older adults. JAMA 278, 659-662 (1997).
Inouye, S.K., Studenski, S., Tinetti, M.E., and Kuchel, G.A.: Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J. Am. Geriatr. Soc. 55, 780-791 (2007).
Janssens, J.P.: Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. Clin. Chest Med. 26, 469-484 (2005).
Jones, C.M., and Boelaert, K.: The Endocrinology of Ageing: A Mini-Review. Gerontology 61, 291-300 (2015).
Kekki, M., Samloff, I.M., Ihamaki, T., Varis, K., and Siurala, M.: Age- and sex-related behaviour of gastric acid secretion at the population level. Scand. J. Gastroenterol. 17, 737-743 (1982).
Kingsberg, S.A.: The impact of aging on sexual function in women and their partners. Arch. Sex. Behav. 31, 431-437 (2002).
Kirkland, J.L.: Translating the Science of Aging into Therapeutic Interventions. Cold Spring Harb. Perspect. Med. 6, a025908 (2016).
Kirkland, J.L., Tchkonia, T., Zhu, Y., Niedernhofer, L.J., and Robbins, P.D.: The Clinical Potential of Senolytic Drugs. J. Am. Geriatr. Soc. 65, 2297-2301 (2017).
Kitzman, D.W., Scholz, D.G., Hagen, P.T., Ilstrup, D.M., and Edwards, W.D.: Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. Mayo Clin. Proc. 63, 137-146 (1988).
Klostermann, E.C., Braskie, M.N., Landau, S.M., O'Neil, J.P., and Jagust, W.J.: Dopamine and frontostriatal networks in cognitive aging. Neurobiol. Aging 33, 623.e15-623.e24 (2012).
Kricun, M.E.: Red-yellow marrow conversion: its effect on the location of some solitary bone lesions. Skeletal Radiol. 14, 10-19 (1985).
Kuk, J.L., Saunders, T.J., Davidson, L.E., and Ross, R.: Age-related changes in total and regional fat distribution. Ageing Res. Rev. 8, 339-348 (2009).
Lamberts, S.W., van den Beld, A.W., and van der Lely, A.J.: The endocrinology of aging. Science 278, 419-424 (1997).
Lasch, H., Castell, D.O., and Castell, J.A.: Evidence for diminished visceral pain with aging: studies using graded intraesophageal balloon distension. Am. J. Physiol. 272, G1-3 (1997).
Latimer, C.S., Keene, C.D., Flanagan, M.E., Hemmy, L.S., Lim, K.O., White, L.R., Montine, K.S., and Montine, T.J.: Resistance to Alzheimer Disease Neuropathologic Changes and Apparent Cognitive Resilience in the Nun and Honolulu-Asia Aging Studies. J. Neuropathol. Exp. Neurol. 76, 458-466 (2017).
Liem, A.T., Keunen, J.E., van Norren, D., and

van de Kraats, J.: Rod densitometry in the aging human eye. Invest. Ophthalmol. Vis. Sci. 32, 2676-2682 (1991).

Lindau, S.T. and Gavrilova, N.: Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. BMJ 340, c810 (2010).

Lindeman, R.D., Tobin, J., and Shock, N.W.: Longitudinal studies on the rate of decline in renal function with age. J. Am. Geriatr. Soc. 33, 278-285 (1985).

Lipschitz, D.A., Udupa, K.B., Milton, K.Y., and Thompson, C.O.: Effect of age on hematopoiesis in man. Blood 63, 502-509 (1984).

Locquet, M., Beaudart, C., Reginster, J.Y., Petermans, J., and Bruyere, O.: Comparison of the performance of five screening methods for sarcopenia. Clin. Epidemiol. 10, 71-82 (2018).

Marshall, B. J.: Helicobacter pylori. Am. J. Gastroenterol. 89, S116-128 (1994).

Mitchell, G.F.: Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J. Appl. Physiol. (1985) 105, 1652-1660 (2008).

Montagna, W. and Carlisle, K.: Structural changes in ageing skin. Br. J. Dermatol. 122, Suppl. 35, 61-70 (1990).

Narici, M.V. and Maffulli, N.: Sarcopenia: characteristics, mechanisms and functional significance. Br. Med. Bull. 95, 139-159 (2010).

Olivetti, G., Melissari, M., Capasso, J.M., and Anversa, P.: Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ. Res. 68, 1560-1568 (1991).

Panda, A., Arjona, A., Sapey, E., Bai, F., Fikrig, E., Montgomery, R.R., Lord, J.M., and Shaw, A.C.: Human innate immunosenescence: causes and consequences for immunity in old age. Trends Immunol. 30, 325-333 (2009).

Park, D.C., Lodi-Smith, J., Drew, L., Haber, S., Hebrank, A., Bischof, G.N., and Aamodt, W.: The impact of sustained engagement on cognitive function in older adults: the Synapse Project. Psychol. Sci. 25, 103-112 (2014).

Parlesak, A., Klein, B., Schecher, K., Bode, J.C., and Bode, C.: Prevalence of small bowel bacterial overgrowth and its association with nutrition intake in nonhospitalized older adults. J. Am. Geriatr. Soc. 51, 768-773 (2003).

Pinto, A., De Filippi, R., Frigeri, F., Corazzelli, G., and Normanno, N.: Aging and the hemopoietic system. Crit. Rev. Oncol. Hematol. 48, S3-S12 (2003).

Ramos-Casals, M., Brito-Zeron, P., Lopez-Soto, A., and Font, J.: Systemic autoimmune diseases in elderly patients: atypical presentation and association with neoplasia. Autoimmun. Rev. 3, 376-382 (2004).

Ray, D. and Yung, R.: Immune senescence, epigenetics and autoimmunity. Clin. Immunol., In press (2018).

Reinders, I., Murphy, R.A., Koster, A., Brouwer, I.A., Visser, M., Garcia, M.E., Launer, L.J., Siggeirsdottir, K., Eiriksdottir, G., Jonsson, P.V., Gudnason, V., and Harris, T.B.: Muscle Quality and Muscle Fat Infiltration in Relation to Incident Mobility Disability and Gait Speed Decline: the Age, Gene/Environment Susceptibility-Reykjavik Study. J. Gerontol. A Biol. Sci. Med. Sci. 70, 1030-1036 (2015).

Salles, N.: Basic mechanisms of the aging gastrointestinal tract. Dig. Dis. 25, 112-117 (2007).

Salvi, S.M., Akhtar, S., and Currie, Z.: Ageing changes in the eye. Postgrad. Med. J. 82, 581-587 (2006).

Schmucker, D.L.: Age-related changes in liver structure and function: Implications for disease? Exp. Gerontol. 40, 650-659 (2005).

Seftel, A.D.: From aspiration to achievement: assessment and noninvasive treatment of erectile dysfunction in aging men. J. Am. Geriatr. Soc. 53, 119-130 (2005).

Smith, C.H., Boland, B., Daureeawoo, Y., Donaldson, E., Small, K., and Tuomainen, J.: Effect of aging on stimulated salivary flow in adults. J. Am. Geriatr. Soc. 61, 805-808 (2013).

Sotaniemi, E.A., Arranto, A.J., Pelkonen, O., and Pasanen, M.: Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin. Pharmacol. Ther. 61, 331-339 (1997).

Stam, H., Hrachovina, V., Stijnen, T., and Versprille, A.: Diffusing capacity dependent on lung volume and age in normal subjects. J. Appl. Physiol. (1985) 76, 2356-2363 (1994).

Stout, M.B., Justice, J.N., Nicklas, B.J., and Kirkland, J.L.: Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. Physiology (Bethesda) 32, 9-19 (2017).

Strenk, S.A., Strenk, L.M., and Koretz, J.F.: The mechanism of presbyopia. Prog. Retin. Eye Res. 24, 379-393 (2005).

Tarlatzis, B.C. and Zepiridis, L.: Perimenopausal conception. Ann. NY Acad. Sci. 997, 93-104 (2003).

Tarnawski, A.S., Ahluwalia, A., and Jones, M.K.: Increased susceptibility of aging gastric mucosa to injury: the mechanisms and clinical implications. World J. Gastroenterol. 20, 4467-4482 (2014).

Tran, L. and Greenwood-Van Meerveld, B.: Age-associated remodeling of the intestinal epithelial barrier. J. Gerontol. A Biol. Sci. Med. Sci. 68, 1045-1056 (2013).

Uitto, J.: The role of elastin and collagen in cutaneous aging: intrinsic aging versus photoexposure. J. Drugs Dermatol. 7, s12-16 (2008).

Valdivieso, V., Palma, R., Wunkhaus, R., Antezana, C., Severin, C., and Contreras, A.: Effect of aging on biliary lipid composition and bile acid metabolism in normal Chilean women. Gastroenterology 74, 871-874 (1978).

van der Zee, E.A.: Synapses, spines and kinases in mammalian learning and memory, and the impact of aging. Neurosci. Biobehav. Rev. 50, 77-85 (2015).

Van Haeringen, N.J.: Aging and the lacrimal system. Br. J. Ophthalmol. 81, 824-826 (1997).

Veldhuis, J.D.: Altered pulsatile and coordinate secretion of pituitary hormones in aging: evidence of feedback disruption. Aging (Milano) 9, 19-20 (1997).

Wade, P.R., and Hornby, P.J.: Age-related neurodegenerative changes and how they affect the gut. Sci. Aging Knowledge Environ. 2005, pe8 (2005).

Wilson, R.S., Beckett, L.A., Barnes, L.L., Schneider, J.A., Bach, J., Evans, D.A., and Bennett, D.A.: Individual differences in rates of change in cognitive abilities of older persons. Psychol. Aging 17, 179-193 (2002).

Yaar, M. and Gilchrest, B.A.: Skin aging: postulated mechanisms and consequent changes in structure and function. Clin. Geriatr. Med. 17, 617-630 (2001).