Chapter 1

Aging and Senescence

BASICS

OVERVIEW

While the adage "Age is not a disease" may be true, the process of aging can be considered one of the most important, and potentially modifiable, causes of disease, disability, and death in adult dogs. (McKenzie) A set of complex but comprehensible processes increase with time that result in a progressive loss of function, a decrease in reserves and recovery capacities, that put the individual at risk for disease and even death. Anticipated, "normal" aging processes need to be distinguished from pathological issues ("non-programmed disruptions of aging")[1] with attempts for coordinated management.

The chronological age of our patients is a major factor, yet it is the individual's response that can greatly influence biological or physiologic age. The ultimate goal is to minimize the impacts of aging changes to maintain health, resilience, and functional capacity for as long as possible (healthspan). Recently, there has been a growing recognition that geroscience approaches in veterinary medicine can have a much greater impact on health and disease burden than traditional biomedical strategies aimed at treating individual diseases in isolation. (Kaeberlein)

Much of the research on aging and associated issues comes from human medicine and laboratory animal data, but there is a growing field of information concerning dogs and even cats. In fact, there is so much literature in this field that this chapter can only present an abbreviated listing of some of the most pertinent facts. When possible, specific dog and cat data is presented.

Terms Defined

- Aging is the decline and deterioration of functional properties at the cellular, tissue, and organ levels. This loss of functional properties yields a loss of homeostasis and decreased adaptability to internal and external stress yielding an increased vulnerability to disease and mortality. (Fedarko)
- Chronological age—actual "calendar" age of the individual
- Biological (genetic) age—how old your cells and tissues are based on physiological parameters—to provide the predicted longevity.
- Lifespan—actual number of years an individual is alive.
- Healthspan—the time an individual is able to maintain good health with a short period of morbidity before death.
- Geroscience refers to research aimed at understanding the mechanisms of biological aging, defining the genetic, epigenetic, and environmental features that determine the rates of aging.[2]

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Companion website: www.wiley.com/go/lobprise/Senior

- Robustness—the ability to maintain optimal physiological function in the face of external stressors.
- Resilience—the ability to return to baseline following stressor disturbance.
- Frailty—a syndrome characterized by the decrease in physiologic reserves, cognitive performance, and dysregulation of multiple body systems with an increased vulnerability to stressors.
- Functional capacity a direct measure of the ability of cells, tissues, and organ systems to operate properly/optimally and is influenced by both genes and environment.
- Senescence—cellular response that blocks further proliferation and alters the cell's phenotype.
- Immunosenescence—the decline in the function of the adaptive immune system that occurs during aging and is associated with thymic involution, alterations in T cell subsets, and reduction in antibody production.
- Inflammaging—the term used to describe the pro-inflammatory state associated with aging.[3]
- Apoptosis—cellular response to remove damaged or aberrant cells through controlled cell death with no inflammatory response.
- Oxidative stress (OS)—the imbalance between free radicals and antioxidants in the body that can cause damage and disease.

ISSUES AND OPTIONS

The "Normal" Aging Process

- Mechanisms of cellular maintenance include:
  - DNA repair
  - synthesis and fidelity surveillance
  - detection and clearance of defective proteins and lipids
  - clearance of defective organelles and cells
  - defense against pathogens and injury
- Main contributors to mammalian aging (Jiminez, Lopez-Otin, Sandor)
  - Genomic instability—damaged with age by mutations, chromosome rearrangement, and increase in copy number variants (CNV)
    - Hinders cell function resulting in cellular senescence, apoptosis, or even malignancy
      - Increased apoptosis can lead to atrophy, or decreased removal of accumulation of senescent cells.
    - Deficiencies in DNA repair
    - Oxidative damage from reactive oxygen species (ROS), free radicals that target DNA, lipids, and protein
      - Oxidative DNA lesions increase with age and with decreased expression of antioxidant enzymes—neurodegeneration
    - Optimal levels of oxidation are needed; they should not be completely irradicated. ROS at low levels are important signaling molecules.
    - Transposable element—transponsons increase with age; can be induced by stressors—heavy metal toxins, genotoxic agents, and nutrition.
    - Assessing when mitochondrial DNA mutations first appear (especially in larger breed dogs), may be helpful in assessing aging and age-related diseases.[4]

- Telomere attrition—the protective portions at the ends of chromosomes that shorten with each cell division in somatic cells (not in germ line cells—they have sufficient telomerase)
    - Limits the number of cycles (Hayflick limit) and correlates with lifespan.
    - May limit the growth of malignant cells but can also contribute to tumorigenesis if chromosomes link end-to-end.
    - Telomeres shorten faster under conditions of chronic inflammation and oxidative stress in humans and animals;[5] even associated with feline chronic kidney disease.[6]
    - Comprehensive lifestyle changes could stabilize telomeres and decrease oxidative stress.
    - Telomeric restriction fragments may vary by dog breed, so this should be considered in evaluation.[7, 8]
- Epigenetic alterations—mechanisms that modulate gene expression and transcription
    - DNA is packed into dense chromatin—heterochromatic or more open euchromatic; their ratio is associated with aging.
    - Methylation of cytosines may block transcription
        - Hyperactive for pro-aging genes but repressing anti-aging genes
    - Regulation by various enzymes working on sirtuin genes—longevity impact
    - Age-related changes—alter mRNA transcriptome: gero-miRNAs (microRNAs) target other longevity miRNAs.
    - Epigenetic regulation may be dog breed specific.[9]
- Proteostasis disruption of proteome (all protein types in a cell)
    - Cell senescence and proteinopathies—accumulation of misfolded proteins
    - Aberrant proteins (altered by glycation) can induce inflammation.
    - Chaperones and protein quality control facilitate appropriate folding of maturing proteins and protect them; these are reduced with aging.
        - Heat-shock proteins (Hsp)—upregulation can extend lifespan in mice
        - Not always protective—can be neurodegenerative
    - Ubiquitin–Proteasome (UPS)—performs selective removal of misfolded and senescent proteins—linked to longevity
    - Autophagy—targets diseased mitochondria and large protein aggregates, fuses with lysosomes and degrades/recycles components
        - If impaired—can be a major factor in aging regulation.
        - Lipofuscin (aging pigment) can accumulate in lysosomes due to oxidation of unsaturated fatty acids. These are insoluble and refractile to cellular removal, compromise organelle function.
- Nutrient-sensing deregulation—nutrients used for cell metabolism, protein synthesis, autophagy
    - TOR—target of rapamycin kinase—determines rates of protein turnover and metabolism
        - Rapamycin—approved immunosuppressant, transplant rejection drug but has severe side effects at medical dosages
        - Increased lifespan seen with a decrease of mammalian mTOR—smaller dosage without side effects
        - Main signaling—insulin and IGF1 signaling pathways
    - FOXO (forkhead box O)—role in tumor suppression and age-related diseases

    - Sirtuins and nicotinamide adenine dinucleotide (NAD)-dependent factors.
    - AMPK (5′AMP-actived protein kinase)—detects levels of AMP, counteracts IGF1 by inhibiting TOR and activating FOXO3a—neuroprotective role.
    - Therapy potential—metformin and acarbose (anti-diabetic medications)—exert anti-aging effect with mild effects at correct dose in dogs.
    - The metabolome (the collection of metabolites in a cell or organism) was analyzed in a caloric restriction study on Labradors to help assess metabolic steps that may impact longevity.[10]
- Mitochondrial dysfunction—main source of energy; mitochondrial respiration generates ATP but also ROS
    - Dysfunction is a main driver of neurodegeneration in humans and dogs
        - In a study, antioxidant diet with mitochondrial co-factors (lipoic acid [LA] and carnitine) improved respiration and reduced ROS.[11]
        - Differing study results may be due to baseline nutrition or possible differences across dog breeds.
    - Advanced glycation end-product (AGE) is formed at the end stage of carbohydrate metabolism and can accumulate in long-lived proteins (collagen) with damage to macromolecules, though there is little research in dogs.
        - Oxidative stress may be involved in AGE formation and AGE may induce OS.[12]
    - Altered mitochondrial homeostasis (mihormesis) may benefit from mild stressors to benefit cellular health and longevity as a defense mechanism.
    - Resveratol and metformin might be mild mitochondrial toxins, inducing mihormesis.
    - High genetic variability—may be challenging to target treatment
- Cellular senescence—permanent cell-cycle arrest with phenotypic changes
    - Phenotype—larger cell, senescence-associated Beta-galactosidase, proteases, cell-cycle inhibitors and pro-inflammatory cytokines.[13]
    - Impacted through DNA damage, oncogene expression and supermitogenic signals; cytoskeletal, interferon-related, insulin-like growth factor (IGF)-related, MAP (mitogen-activated protein) kinase, and oxidative stress pathways.
    - Correlates with chronologic age (biomarker)
    - Accumulation in tissue as innate immune system declines with age and less phagocytosis.
    - Produce inflammatory signals, special inflammatory microenvironment around themselves—induce senescence in neighboring cells—bystander effect
- Stem cell exhaustion—tissue renewal depends on tissue-specific stem cells
    - Increase in cell senescence may initially activate stem cells, then they become depleted—accelerates aging
    - Stem cells may also decrease in ability to replicate and differentiate—e.g., in old age anemia.
    - Stem cell therapy potential—especially for neurodegenerative diseases
- Altered intercellular communication and Inflammation
    - Paracrine, endocrine, and neurocrine signaling
    - Growth hormone (GH), insulin/IGF1 (somatotropic axis), supervised by HPA (hypothalamus–pituitary–adrenal) axis and thyroid axis; hormones from digestive and reproductive systems, small molecules from gut bacteria
    - Neuroendocrine signaling—neural aging—a central mechanism

- BDNF (brain-derived neurotrophic factor) and serotonin affect brain aging; changes due to caloric restriction
- Hypothalamus—reproductive aging controlled by GnRH (gonadotropin-releasing hormone)
  - Reduction in response to inflammation can aggravate frailty
- Extracellular vesicles—exosomes and ectosomes
  - Released into blood—transducers of cellular signals and their content
    - miRNAs—diagnostic and prognostic measures of some diseases
    - Stem cells of hypothalamus—exosome miRNAs may modulate aging and neurodegeneration

- Inflammaging and immunosenescence (see inflammaging; see immunosenescence)
- Microbiome—systemic and immune function can be modulated by bacteria in the gut
  - Various chemical signals may affect organs (brain) and aging
    - Oral microbiota and inflammation are linked to Alzheimer's disease.
  - Probiotics and prebiotics that can beneficially alter the biome have been reported to positively influence the aging of the gut and systemic inflammation in people.[14]

Immunosenescence

- Adaptive immunity declines, low-level, chronic activation of innate immunity systems leads to low-level, chronic pro-inflammatory state
  - Reduced naïve CD8+ T-cells and moderately elevated memory T cells
  - Bone marrow–derived macrophages lose their phagocytic capacity.
  - Altered cytokines can facilitate disease progression
  - Cardiovascular disease, cancer, diabetes mellitus, osteoporosis, rheumatoid arthritis, and cognitive disorders in humans can all be impacted.

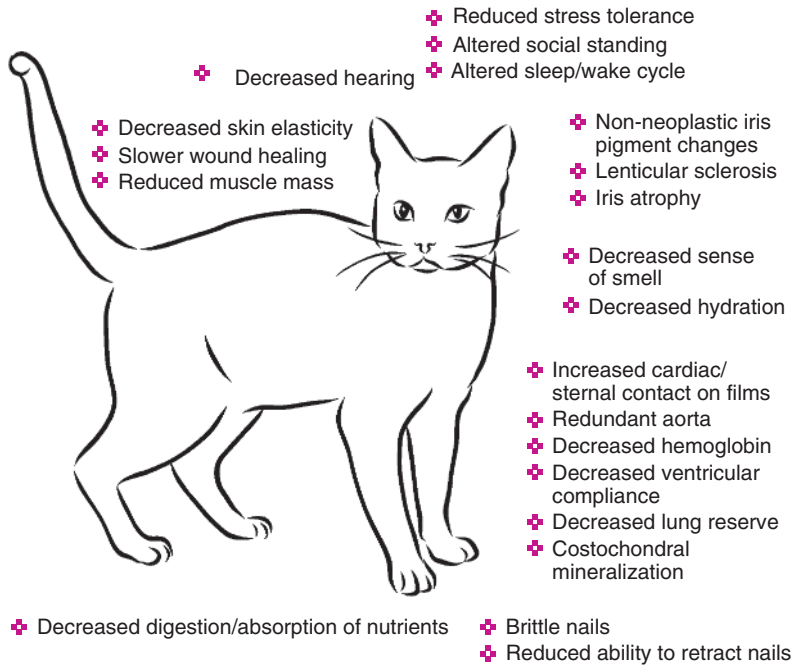
Inflammaging

- Acute inflammation is important for response to stressors
- Chronic, "sterile," inflammation - pro-inflammatory state, elevated IL-6 levels
  - Cytokines affect growth hormone/IGF-1 (somatotrophic) axis
  - "Sickness behavior"—fatigue, malaise, loss of interest in social, difficulty concentrating, sleep pattern changes.[15]
  - Neuromodulators—depressive disorders
  - Hypothalamic–pituitary–adrenal (HPA) axis hyperactivity—cytokines disturb the negative feedback inhibition of corticosteroids.[16]

The "Appearance" of Aging in Senior Pets

- As individuals travel through their life stages, the rapid increase in robustness and resilience from birth to maturity levels off during the mature adult stage. Past this mature stage, the physical and functional changes due to the aging process start to become apparent. (See Figure 1.1)
- There are many changes occurring in the aging pet—appearance and function
  - Phenotypic changes (Figure 1.2)
    - Fur or coat—graying, thinning, texture; possible decrease in grooming.
    - Skin—pigmentation, wrinkling, loss of elasticity.

■ **Figure 1.1** The phenotype of aging may occur slowly, but comparing young and old pets, or comparing the older pet to earlier photographs, can make these changes more apparent. Source: With permission of Shannon Strauss.



■ **Figure 1.2** Changes associated with aging (and often seen in apparently healthy senior cats). Source: Reprinted from Ray et al.[17].

- Dental disease can be accumulative, but influenced by many factors, not a reliable indicator of age.
- Neoplasia—predisposed to cellular and biochemical changes due to aging factors, but other factors as well.
- Musculoskeletal

        - Muscle mass loss
            - Generalized sarcopenia as a "normal" aging change.[18]
            - Replacement by fat, increase in visceral fat
        - Unintentional weight loss[19]
        - Joint degeneration: other factors may have begun the process, but progressive deterioration
        - Loss of strength and mobility
    - Sensory—auditory, visual, olfactory
    - Organ structure and function
        - Gastrointestinal—
            - Reduced salivary and gastric acid secretion, digestive enzyme function.
            - Intestinal epithelium structure and turnover.
            - GI microbiome (see above)
            - If no specific disease, dogs maintain digestive capacity; protein and fat digestion can decrease in cats.
        - Heart, lungs, kidneys
            - Heart—decreased elasticity and loss of functional capacity
            - Lungs—morphology, elasticity, and functional changes
            - Renal—glomerulosclerosis, interstitial inflammation, and fibrosis; decreased GFR.
        - Endocrine—many changes, not all are well-documented
            - HPA (hypothalamus–pituitary–adrenal) axis – stress responses changed.
            - Thyroid and insulin-like growth factor decline
        - Immune system—see above
    - Behavior
        - Social behavior—also in cognitively unimpaired pets
            - Fearful responses or aggression—rule out pain, physical and sensory disabilities.
        - Activity—less active, less exploratory, sleep more
            - Hard to distinguish between sensory impact and cognition
            - Increase in aimless activity—cognitive, pain, or sleep imbalance
        - Cognitive deficits (see CDS—cognitive dysfunction syndrome)—wide range of changes
        - Elimination issues—house-soiling; of great concern to owners
            - Difficulties in mobility or posturing to eliminate
            - "Lose" their training
        - Vocalization—perceived as a sign of discomfort; pain should be ruled out.
- Changes are highly individualized
- The numbers of "super-seniors"—those living longer than an estimated life expectancy—continues to expand with many pets reaching lifespans that were considered exceptional in the past.[20]

Aging "Clocks"

- Epigenetic clocks
- Some aspects of the genome can change within the course of an individual's lifespan including patterns of DNA methylation, a hallmark of aging.
- Mammalian methylation array—conserved across all species.[21]

- Can predict chronological age and some aspects of biological age.[21]
  - In one study, did not relate well to breed weight or breed lifespan
  - DNAm Average Time to Death assessment predicts average time to death with a positive correlation to breed lifespan and negative correlation to breed weight.
- Useful biomarker in age-extending research and in understanding dog breed differences. [22, 23]
- Clocks based on Frailty[24] (see Frailty)
- The Frailty Index (FI) for humans is a strong predictor of morbidity and mortality
- A study looked at frailty models in mice
  - FRIGHT (Frailty-Inferred Geriatric Health Timeline) clock, a strong predictor of chronological age, not predicting time to mortality
  - AFRAID—Analysis of Frailty and Death—accurately predicts life expectancy and efficacy of intervention
  - Individual frailty items vary in their correlation with age, some items weighted.
  - Able to assess impact of interventions such as administering enalapril and restricting methionine.

Canine Geriatric Syndrome (CGS)

- McKenzie and others have proposed a framework for advancing research in veterinary geroscience.[24]
- "CGS consists of the multiple, interrelated physical, functional, behavioral, and metabolic changes that characterize canine aging as well as the resulting clinical manifestations, including frailty, diminished quality of life, and age-associated disease."
  - Physical changes
  - Clinical disease
  - Functional changes
  - Frailty
  - Metabolic changes
  - Quality of Life and Caregiver burden
- They have also proposed key components of an assessment tool that "would facilitate the development and testing of interventions to prolong health span and lifespan in dogs by directly targeting the biological mechanisms of aging."[6]

Client Communication

- Throughout the lifestages of the pet, it is important to educate the client as to the expected changes that occur within each time frame, and the level of care needed.
  - Providing a continuum of care including preventive care and early detection of specific issues can minimize the impact of aging and disease.
  - Emphasizing that the "geroscience approach" to manage all aspects of the pet's lifestyle (exercise, diet, enrichment, etc.) can have as much of an impact as disease management.
  - It is inevitable that these changes will happen, and we should advocate with the owners to enhance the healthspan of the patient.
- Many impairments can impact comfort, function, and quality of life (QoL) even without specific diseases identified.
  - QoL is often a primary factor in end-of-life (EOL) decisions.
  - Aging impacts both healthspan and lifespan.
  - The human–animal bond can be greatly stressed with ongoing emotional, physical, and financial costs to the owner. Caregiver burden has many aspects and is different for every situation (see Caregiver Burden)

See Also

- Cognitive Dysfunction Syndrome (CDS)
- Frailty
- Immunosenescence
- Inflammaging

Abbreviations

- AFRAID = Analysis of Frailty and Death
- AGE = Advanced glycolation end-product
- AMPK = 5′AMP-actived protein kinase
- ATP = Adenosine triphosphate
- BDNF = brain-derived neurotrophic factor
- CD8 = cytotoxic T-cell lymphocyte with CD8 dimeric co-receptor
- CDS = cognitive dysfunction syndrome
- CNV = copy number variants
- CGS = Canine Geriatric Syndrome
- EOL = end-of-life
- FI = Frailty index
- FRIGHT = Frailty Inferred Geriatric Health Timeline
- FOX = forkhead box O
- GnRH = gonadotropin-releasing hormone
- GFR = glomerular filtration rate
- GH = growth hormone
- HPA = hypothalamus–pituitary–adrenal axis
- Hsp = heat-shock protein
- IGF = insulin growth factor
- IL = interleukin
- LA = lipoic acid
- MAP kinase = mitogen-activated protein kinase
- miRNA = microRNA
- NAD = nicotinamide adenine dinucleotide
- OS = oxidative stress
- QoL = quality of life
- ROS = reactive oxygen species
- TOR = target of rapamycin kinase
- UPS = ubiquitin proteasome

Reading List

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