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The phenotype of aging in the dog: how aging impacts the health and well-being of dogs and their caregivers

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ABSTRACT

Aging is the single most important cause of disease, disability, and death in adult dogs. Contrary to the common view of aging as a mysterious and inevitable natural event, it is more usefully understood as a set of complex but comprehensible biological processes that are highly conserved across species. Although the phenotypic expression of these processes is variable, there are consistent patterns both within and between species.

The purpose of this feature is to describe the patterns currently recognized in the physical and behavioral manifestations of aging in the dog and how these impact the health and welfare of companion dogs and their human caregivers. Important gaps in our knowledge of the canine aging phenotype will be identified, and current research efforts to better characterize aging in the dog will be discussed. This will help set the context for future efforts to develop clinical assessments and treatments to mitigate the negative impact of aging on dogs and humans.

What Is Aging?

For a phenomenon we all experience, aging is challenging to define precisely. It involves changes that occur over time, but time is not necessarily the primary driver of those changes. Aging can be understood from the perspective of philosophy, sociology and psychology, evolutionary biology, or even thermodynamics. For veterinarians and our patients, however, it is most useful to understand aging from a biomedical perspective. In this context, aging can be thought of as "the progressive accumulation of changes with time associated with or responsible for the ever-increasing susceptibility to disease and death."[1]

Debates have raged for decades about the phrase "responsible for" in this definition and about the distinction between what constitutes normal aging and disease,[2,3] but for practical purposes it is sufficient to recognize that individuals experience progressive loss of function, greater risk of certain types of disease, and a greater likelihood of death as their chronological age increases. We can call this overall process "aging" and use it as a starting point for studying the phenomenon without having a perfect understanding of the distinction between healthy aging and disease or the complex relationship between time and the changes that accompany its passage.

Aging involves a myriad of processes at multiple levels, from the molecular to the organismal, that affect an animal's function and susceptibility to disease and death. There are patterns to these changes that are often conserved across species. However, aging is also a variable and individual process. Biologically, some individuals age faster than others in terms of the onset and progression of specific physical, behavioral, and cellular or biochemical manifestations of aging. Biological age is related to but not synonymous with chronological age. This is especially clear in dogs, the larger of which typically experience deleterious consequences of aging earlier and die younger than dogs of smaller body size.[4–7]

The field of aging biology is well established in the laboratory research domain, and we have extensive knowledge of core aging mechanisms in many species, including dogs. Efforts to translate this knowledge into preventative and therapeutic interventions are beginning to proliferate rapidly, and there are many promising avenues for future research. The goal is to prolong life span (the number of years an individual lives) and health span (the number of years free of significant disease or disability).

Regardless of the number of years lived, all dogs progress through a life cycle that involves changes in physiologic and functional capacity over time. There is a rapid increase in robustness (the ability to resist deviation from an original or optimal state) and resilience (the ability to return to this state after deviations induced by external stressors) from birth to physical maturity.[8] The inevitable decline in health and function that follows can occur along variable trajectories **(Figure 1)**. The purpose of interventions to promote healthy aging is not only to increase the number of years lived but to maximize the period of good health and confine the loss of resilience and functional capacity to the shortest possible period.

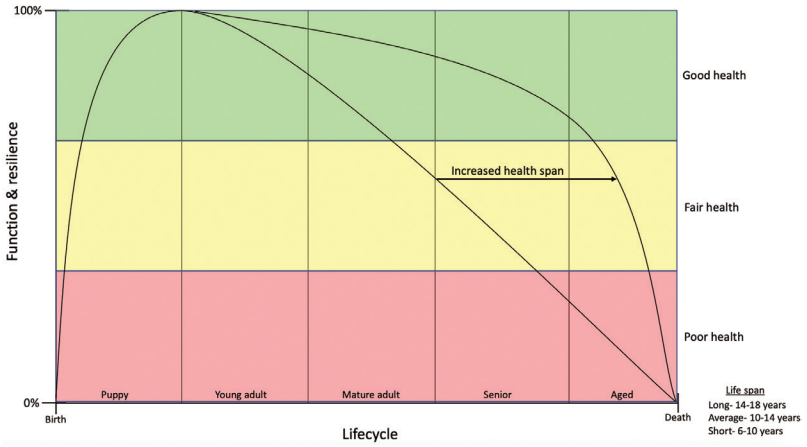

Figure 1—Life cycle trajectories with varying health span in dogs. Antiaging therapies can increase life span (years lived) and health span (years lived in good health) by delaying the onset of age-associated disease and disability (life span ranges are drawn from limited available studies reporting canine longevity data[9–12]).

Therapies that delay death but do not prolong health span can reduce overall quality of life by prolonging the period of disability preceding death. Short-lived breeds appear to age more rapidly than longer-lived breeds and experience both earlier onset of age-associated disease and earlier death. While such breeds will benefit most from therapies that prolong life, both short-lived and long-lived breeds will benefit from extending health span.

The purpose of this manuscript is to briefly summarize current knowledge about the clinical phenotype of aging in dogs and how this impacts health, quality of life, and the human-animal bond. This will provide context for ongoing and future efforts to develop and test therapies to extend health span and life span. An additional aim is to challenge the common understanding of aging as inevitable and immutable and encourage veterinarians to view it as the single most important modifiable risk factor for chronic disease. A companion review in the June 2022 issue of the *American Journal of Veterinary Research* focuses on mechanisms of aging at the molecular, cellular, and tissue levels. (Although aging is of equal clinical importance in other companion animal species and some authors have suggested that the cat may be as apt a translational model of aging in humans as the dog,[13] this manuscript focuses on canine aging both in the interest of maintaining a manageable scope and because the literature concerning the phenotype of aging in cats[14,15] and most other species is very sparse.)

Physical Hallmarks of Canine Aging

Although there are significant differences in the onset and rate of aging in large and small dogs, there are common physical changes seen in nearly all dogs as they age. Many of these are seen in humans and other mammals as well. Age-associated changes in appearance and function are readily recognized by clinicians and owners, but there is limited research documenting the frequency, timing, or causal pathways of these changes. We can often identify an old dog of any breed through a gestalt assessment of appearance, movement, and demeanor without being able to detail all the specific features that signal age. One interesting challenge for canine aging science is to be able to break this assessment down into components and quantify phenotypic markers of biological aging.[16]

Aging dogs develop graying and thinning of hair as well as characteristic changes to coat texture.[3,17–19] Increased pigmentation, wrinkling, and loss of elasticity in the skin are also common in older dogs, though pathologies such as allergic dermatitis, sun exposure, and other factors can contribute to such changes as well. Calluses and hyperkeratosis of the footpads are frequently reported as an age-associated change in dogs, though this is influenced by activity and the substrate on which dogs commonly rest or walk.[18,19]

Dental disease is frequently used as an indicator of age because calculus and tooth wear tend to accumulate over time.[20,21] However, the rate of calculus accumulation and enamel wear and the extent of gingivitis and periodontitis in an individual dog are affected by many factors other than age, including genetics, diet and chewing behavior, and, of course, dental care. Due to the multifactorial nature of dental pathology, it is not a consistently reliable indicator of aging.

Older dogs are more likely to develop both benign and malignant neoplasms, and an accumulation of cutaneous and subcutaneous masses is often associated with aging.[18,19,22] While the specific neoplasms developed by individual dogs are determined by breed-specific genetic risk factors and environmental influences, the overall incidence of neoplasia is an age-related phenomenon. Cocker Spaniels, for example, may be more likely to develop papillomas as they age while Labrador Retrievers seem more likely to get lipomas, but both neoplasms are more common in older individuals.[22,23] The progressive development of visible and palpable masses in older dogs is representative of the general pattern of age-associated pathologies; aging predisposes individuals to diseases through cellular and biochemical changes that occur over time, but the onset and specific nature of how these changes manifest are also shaped by factors other than the passage of time.

Some of the most notable changes that characterize aged dogs are musculoskeletal. Loss of visible muscle mass, such as in the epaxial and masticatory muscles, is common, as is generalized sarcopenia.[24] There is a relative increase in the proportion of fat mass in aged dogs, and there may be an overall loss

of weight in the oldest animals.[25] Other musculoskeletal changes include decreased elasticity of connective tissues and development of degenerative changes in joints. These changes contribute to the decline in activity and comfort that is a common and significant concern for owners.

Apart from changes in muscle mass, older dogs lose strength and mobility and develop progressive articular degeneration and osteoarthritis. This is clearly an age-associated condition, but the relative contributions of chronological age compared with other factors such as breed, body weight, nutrition, and neuter status to the timing of onset, progression, and severity of arthritis are not completely clear.[26,27]

The auditory, visual, and olfactory apparatus show age-associated changes similar to those in humans, likely with similar functional effects, though this has not been evaluated in detail.[28–32] Clinically apparent changes include clouding of the lens associated with lenticular sclerosis or age-associated cataracts as well as functional deficits such as loss of hearing. Histologic changes have also been described, but we do not always have tools to evaluate associated functional changes, such as those in olfaction.[33]

Many physical changes occur with age that cannot be seen directly or through obvious functional consequences. The available research reveals changes in organ structure and function similar to those seen in humans or lab animals such as mice. For example, various structural and functional changes for which the clinical significance is unclear occur in the gastrointestinal tract of aging dogs. Older dogs may have reduced salivary and gastric acid secretion, reduced digestive enzyme function in vitro, and changes in the structure and turnover of the intestinal epithelium.[34] A variety of changes in the gastrointestinal microbiome have been reported in older dogs, although no clear universal pattern of change with aging has emerged from this research.[35,36] Few obvious clinical effects of these alterations to the gastrointestinal tract have been documented. Dogs generally require fewer calories and more protein from their diet as they age, but they appear to maintain robust digestive and absorptive capacity in the absence of specific gastrointestinal tract diseases.[35,37]

The heart, lungs, and kidneys also undergo characteristic structural and functional changes with age. There is decreased elasticity and loss of functional capacity during exercise in the hearts of older dogs.[38,39] The lungs of dogs show changes in morphology, elasticity, and functional capacity similar to those seen in aged humans.[40,41] Common age-associated changes reported in the kidneys of aging dogs include glomerulosclerosis, interstitial inflammation and fibrosis, and a decline in glomerular filtration rate.[42]

Age-associated changes are observed in many endocrinological and clinical laboratory parameters in dogs, but the specific pattern and clinical significance of these changes are not well established and results from different studies are sometimes conflicting.[18,38,43,44] For example, the functioning of the hypothalamus-pituitary-adrenal axis and the response to stress differ between old and young dogs.[45,46] Generally, thyroid hormone and levels of growth hormone and insulin-like growth factor 1 tend to decline with age while markers of renal function (eg, BUN) tend to increase.[44–46] Other analytes, such as blood glucose and some liver enzymes, show different patterns of association with age in different studies, indicating that variables other than chronological age also influence these values.

Finally, dogs appear to develop an age-associated decline in immune function similar to the immunosenescence described in humans, although we do not have a detailed or consistent understanding of this process or its clinical significance.[47–49] Some canine immune cells are less responsive to stimulation in the laboratory, and some differences between young and old dogs have also been seen in elements of the humoral immune system. However, older dogs appear adequately responsive to vaccination, and while it is expected that the changes seen in research studies relate to observed differences in susceptibility to infectious disease, autoimmune disease, and neoplasia in dogs, the relationship between age-associated changes in the immune system and the epidemiology of clinical disease is not well characterized.

Behavioral Hallmarks of Canine Aging

In addition to the physical changes experienced by aging dogs, changes in behavior are also seen. However, the distinction between normal age-associated change and pathology is particularly murky in the behavioral domain. For convenience, age-associated changes in dog behavior can be grouped into general categories, though there is significant overlap between them. These include changes in social behavior, activity, cognition, and elimination.

As dogs age, they may become less interactive with humans and other animals. Associations between age and sociability have been demonstrated in both healthy, cognitively unimpaired dogs as well as dogs with age-associated cognitive dysfunction.[50–52] Increases in fearful responses and aggressive behavior sometimes develop with age.[3,53] However, studies showing such changes with age in social and many other types of behavior do not always effectively rule out the influence of physical and sensory disabilities.[54]

Activity levels also commonly change as dogs age. In general, older dogs become less active, show less exploratory and play behavior, and sleep more overall, especially during the daytime.[51–53] Distinguishing between changes in motivation or cognition and age-associated sensory-motor deficits as potential causes for reduced activity, however, is challenging. Other types of activity are often increased in older dogs. Aimless pacing and general restlessness, especially at night, are commonly seen and attributed to cognitive changes, anxiety, disruption of normal sleep-wake cycles, and potential physical discomfort.[3,54,55]

Cognitive deficits can be seen in older dogs in both home environments and laboratory settings. There is a spectrum of such changes from the most subtle, often only detectable in trained assessment

tasks, to the more clinically evident. In laboratory settings, old dogs appear to be less able than young dogs to perform certain kinds of tasks such as those involving spatial memory or more complex tasks such as reversing a previously trained behavior. Other functions, however, may be preserved, such as being able to discriminate between objects with different physical characteristics.[56,57] Cognitive testing provides a more precise understanding of age-associated cognitive change, but the connection between deficits identified in such testing scenarios and real-world functional deficits is unclear.[53,54,58]

In the home environment, subtle cognitive dysfunction may go unnoticed or may be perceived by owners and clinicians as simply normal aging. As cognitive deficits progress, however, dogs may wander or be unable to navigate normally through their physical environment and may appear to get lost or stuck in places or fail to recognize familiar humans or animals.[3,53] These manifestations of aging are more likely to be viewed as pathological or detrimental to quality of life and disrupt the bond between dogs and owners.[59,60]

The changes most often of greatest concern to owners are those involving house soiling. Older dogs may exhibit more inappropriate elimination, and while this is sometimes related to physical difficulties with locomotion or posturing to eliminate, it appears that some previously house-trained dogs lose the ability to distinguish appropriate and inappropriate locations for elimination.[55,58,61]

Owners are also commonly concerned by increased or inappropriate vocalization in aged dogs, which may be disturbing directly and also perceived as a sign of discomfort.[56] Some dogs may cease to be able to perform specific functions expected of them by their owners, such as retrieving, herding, obedience to commands, or other trained work.[53]

The debate about whether some age-associated behavioral changes can be considered normal and reliably distinguished from pathology is contentious. While some authors consider dogs with minimal deficits that do not significantly impact daily life to be examples of "successful aging,"[53] others argue that we do not yet have a clear enough understanding of the relationship between chronological age, anatomic and functional changes in brain function, and behavior to effectively distinguish between normal and accelerated or abnormal aging.[54]

While many changes in behavior and cognitive function are common in most older dogs, they are by no means universal, and the form and timing of onset show great variation. For example, while large dogs have shorter life spans and appear to age faster than smaller dogs in some respects, studies of age-associated cognitive dysfunction are mixed, with some indicating earlier onset in larger dogs and others finding no such association.[53,62,63]

This variability suggests a common set of mechanisms underlying aging that is modified in expression in each individual by both intrinsic and environmental factors. While teasing out these factors is an interesting and productive research challenge, drawing a bright line between healthy and unhealthy aging isn't critical from a clinical perspective. Many of these changes are likely related to common underlying aging mechanisms, and all have at least the potential to impact comfort and function, providing a reason and an opportunity to seek interventions to mitigate the impact of age-associated changes.

Consequences of Aging in Dogs

Aging is a key risk factor for many specific diseases in dogs, including most of the leading causes of canine mortality, as follows: neoplasia, cardiovascular disease, and degenerative neurologic or musculoskeletal diseases.[9,64–66] The aging process is a critical risk factor limiting life span and health span in dogs by triggering common diseases and resulting mortality.

Age-related changes also include the many physical and behavioral impairments described above that reduce comfort, function, and quality of life in dogs. These significantly limit both health span and life span even in the absence of clinically diagnosed diseases. The increased risk of death associated with advancing aging is a function of both specific morbidities and the global decrement in comfort and function for aging dogs.

The majority of companion dogs are euthanized rather than die as a direct result of disease.[10,11,67] Many factors are involved in the decision to euthanize a companion dog, but owners frequently cite the quality of life impairment associated with aging and old age itself as well as specific age-associated diseases as reasons for choosing euthanasia.[59–61,67,68] The global impact of aging, therefore, is a primary determinant of both health span and life span through both increased incidence of age-associated disease and increased risk of euthanasia due to owner perceptions of age-related decrements in function and quality of life.

These consequences of canine aging also significantly impact dog owners and the bond they share with their pets. Age-associated diseases represent a significant emotional and economic cost to dog owners. Studies have indicated that the caregiver burden for owners of pets with chronic disease is high, increasing symptoms of stress, depression, and anxiety and reducing quality of life.[69,70] This is in addition to the costs of care for dogs with age-associated disease and disability, which can be substantial and impact the overall financial and psychological well-being of owners.[71] Finally, when the burden of age-related disease and dysfunction leads owners to choose euthanasia, there is a significant emotional cost to the owner and potentially to veterinary staff as well.[72–75]

Canine Aging Research: Past, Present, and Future

Our evolving understanding of how dogs age has diminished the aura of inevitability associated with aging. Targeting the mechanisms of aging as a collection of modifiable risk factors for disease and death, rather than focusing on treatment of specific diseases, is an approach replete with plausible hypotheses and

promising, although largely still unproven, therapies. There are currently over 500 clinical trials registered on the US NIH Clintrials.gov website testing interventions that target aging and longevity rather than specific clinical diseases.[76] While there are far fewer veterinary aging studies, the field is growing rapidly.

An important step toward mitigating the impact of aging is clarifying the aging phenotype in dogs and exploring the underlying mechanisms. An example of ongoing research on the manifestations of aging and risk factors for age-associated disease is the Morris Animal Foundation Golden Retriever Lifetime Study (GRLS). The GRLS is the first large, prospective, longitudinal cohort study to follow a group of companion dogs throughout their lifetime.[77] The study is collecting comprehensive data about husbandry and clinical disease as well as clinical laboratory samples, which will be banked and available for analysis as genetic and biomarkers for aging and age-related diseases are discovered.

Such cohort studies have been critical to understanding the patterns of aging and the genetic and environmental correlates of age-related diseases in humans, and the GRLS will be an invaluable source of data for future interventional studies of antiaging therapies in dogs. Though the study is expected to last for over a decade, researchers are already analyzing data from the participants and publishing their findings.[78]

Another active effort to understand patterns and causes of aging in dogs is the Dog Aging Project.[79] This project incorporates public participation and controlled research studies, such as investigation of potential antiaging pharmaceutical interventions.[80,81] Survey data are being collected on thousands of dogs, creating awareness of the canine aging biology field among the general public and building a useful database and also a pool of potential subjects in future clinical studies. The project also explicitly approaches research into canine aging as a translational model to support faster development of interventions for humans.

Research is also ongoing into many of the underlying mechanisms of canine aging. One example is the study of epigenetic markers to assess biological age in dogs. Epigenetic changes are modifications to DNA, such as methylation, that influence gene expression. Such changes occur with aging and can have deleterious effects on gene products and health.[82] Epigenetic change has been intensively explored as a potential measure of biological age.

Several epigenetic clocks have been developed to predict chronological and biological age and correlate this with aging in other species, such as wolves and humans.[83,84] This work may eventually enable commercial diagnostic tools to assess and compare the biological ages of individual dogs and different canine populations. Such tools will also be useful in assessing the impact of antiaging interventions.

Promising Strategies for Addressing Aging in Dogs

We can be confident that at least some impacts of aging in dogs can be mitigated by such interventions because this has already been demonstrated in clinical studies. The best-studied and most consistently effective approach for retarding aging and extending health span and life span is dietary restriction. Since the 1930s, numerous studies have shown that reducing overall calorie intake at least 15% to 25% without inducing malnutrition extends life span and reduces age-associated disease dramatically in nearly all species studied, from yeast and fruit flies to rats and primates and, of course, dogs.[85] More recent studies have also found that reduction of specific macronutrients, notably protein, and interventions that target feeding patterns without reducing calories, such as intermittent fasting, can also have life span and health span benefits.[85] However, calorie restriction is still the best-supported antiaging intervention.

A caloric restriction study was conducted in Labrador Retrievers from 1987 through 2001.[86] Forty-eight dogs (24 pairs of littermates) were initially assigned to ad libitum feeding or a calorie intake of 25% less than what the free-fed member of the pair consumed. At 3.5 years of age, the ad libitum fed dogs were switched to a calorie intake intended to maintain an optimal body condition, while the paired littermates continued to receive 25% less than what these dogs consumed. Over the course of the study, significant differences were seen in many of the mechanisms and impacts of aging.

Calorie-restricted dogs lived 15% longer (a difference of 1.8 years) compared to nonrestricted dogs. The illnesses that occurred and causes of death seen were largely the same between groups. However, the dietary-restricted dogs experienced the onset of chronic disease significantly later (a median difference of 2.1 years or 21%), showing that dietary restriction increased health span as well as life span.[86]

This study provides strong evidence that dietary restriction can significantly improve life span and health span in dogs by targeting aging. Additional data supporting this finding has come from a study showing greater-than-expected life span in Labrador Retrievers on restricted-calorie diets.[87]

Although dietary restriction has proven effective in combating the effects of aging in many species, it is not practical as a clinical intervention. A number of other approaches have been investigated in the dog, some of which mimic the effects of dietary restriction and others that target different aging mechanisms.

For example, the mechanistic target of rapamycin is a protein kinase that plays a central role in regulation of energy metabolism, cell growth and proliferation, and many of the common pathways of aging in mammals and other taxa.[85] Inhibition of this target with drugs, notably rapamycin, has been shown to increase life span and retard age-associated disease in laboratory animals, from yeast and roundworms to mice.[80] The mechanism of this improvement in life span and health span mimics, in many ways, the effects of caloric restriction, and rapamycin is a key target of longevity research. A small pilot study of rapamycin in companion dogs found no significant adverse effects,[80] and a larger, longer-term study is in progress.[81]

Research into antiaging therapies for dogs is expanding rapidly. Much of this is driven by the potential of dogs as a translational model for aging therapies in humans.[88–90] Dogs have a high degree of phenotypic and genetic diversity, share our physical and social environments, and experience many of the same patterns of age-associated disease as humans. Dogs also have significant value to their owners as individuals and often receive extensive preventative and therapeutic health care. Effective interventions to delay and mitigate age-associated diseases in dogs will have a market among dog owners and great potential to lead to antiaging interventions for humans, and this incentivizes canine longevity research.

Therapies targeted at prevention and treatment of specific age-associated diseases currently dominate the clinical management of canine aging. While these will remain a critical part of geriatric care, there is tremendous potential to extend health span and life span in dogs with preventative interventions targeting the underlying mechanisms of aging. Doing so can potentially delay or prevent a broad spectrum of age-associated diseases, which may have greater impact on health and longevity than a narrower focus on specific morbidities. The future of canine aging science is to build on the foundational understanding of aging derived from laboratory animal studies to clarify our grasp of the mechanism and phenotype of aging in companion dogs and to develop interventions that reduce the overall occurrence of age-associated disease and the negative impact of aging on quality of life.

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