

Aging Research 2011: Exploring the Pet Dog Paradigm

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Abstract

Researchers are counting on comparative biologists to find alternative animal models of human aging that will foster experimental approaches to study disability-free longevity, not just the addition of years. This article presents one such alternative: the use of pet dogs living in the same environment as people to study the determinants of healthy longevity. There are both theoretical and practical reasons for this research model beyond the well-documented physiologic similarities between dogs and humans. First, a wealth of medical data—based on clinical and biochemical evaluation, medical imaging, and pathology—is available for pet dogs. Second, a vast array of phenotypic domains can be accurately assessed in dogs, ranging from cardiac contractility and glomerular integrity to the ability to climb stairs and interact with people. Moreover, studying pet dogs obviates the purchase and per diem costs typically associated with large animal research. Pet dogs may be particularly well suited for exploring (1) mechanisms of sex differences in longevity; (2) interventions to compress morbidity and enhance healthspan; (3) genomic correlates of successful aging phenotypes and endophenotypes; (4) heterogeneity in resistance to aging-related diseases, such as cancer; and (5) noninvasive biomarkers of particular target organs. Finally, between-breed differences in senescence trajectories and longevity may expand hypotheses of key genetic factors that contribute to sustained organ function and the postponement of disease. Yet the pet dog paradigm in aging research is nascent; tapping into the potential of this model will add to the existing strengths of conventional model systems.

Key Words: animal model; cognitive aging; disease resistance; dog; gene-environment interaction; healthspan; life course; longevity; sex difference

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Introduction

In a 2006 article on the challenges and opportunities in the emerging field of comparative oncology, I described similarities and differences between naturally occurring cancers of dogs and humans to shed light on key issues on the minds of cancer scientists and oncologists (Waters and Wildasin 2006). The paper benchmarked the progress in this field, highlighting pioneering work in pet dogs with bone cancer that contributed to the development of limb-sparing surgeries now used to treat people with this deadly disease. Additionally, it emphasized that conducting careful dose-response studies in dogs led to the realization that more of a “good thing,” such as the essential trace element selenium, might not necessarily be the best thing for an aging prostate. These canine dose-response data provided a plausible explanation for the recent disappointing null results of a large-scale prostate cancer prevention trial involving 32,000 men (Chiang et al. 2010; Lippman et al. 2009).

In this article, I explore a new paradigm—the study of pet dogs—in the field of aging research, describe the prospects and challenges of this alternative approach, and illustrate ways in which dog studies can directly complement work in humans and in conventional model systems. Such research may lead to a deeper understanding of the biology of human healthspan.

Historical Perspective

Dogs are credited with opening many new research vistas that have had profound impact on human health. Each landmark success capitalized on the striking similarities between the physiology of humans and dogs. In the toxicology field, scientists have turned to laboratory beagles for decades to evaluate chemical exposures and make inferences about human safety. Less visible, but equally compelling, is the prospect that pet dogs may be effective biomonitors of important environmental exposures (Waters and Wildasin 2006). For example, dogs living in the same household as an asbestos-exposed human develop mesothelioma not only at an increased frequency but also decades before it strikes the exposed human (Glickman et al. 1983).

In the early 1900s, dogs played a pivotal role in the discovery that the pancreas was an integral player in blood glucose regulation. By preparing extracts from duct-ligated canine pancreas (resulting in the atrophy of the digestive juice-laden exocrine portion), Banting and colleagues

developed the first effective treatment for diabetes mellitus and ultimately made the discovery of insulin (Bliss 1982).

A few decades later, Huggins showed that surgical removal of the testes of dogs provoked involution of the prostate (Huggins and Clark 1940). The stalwart androgen dependence of the dog prostate prompted him to conduct studies in men with prostate cancer, revealing that human prostate cancers could be regressed by surgical castration (Huggins and Hodges 1941). This work provided the platform for pharmacological androgen ablation that is the mainstay of human prostate cancer therapy today.

With this sizable legacy squarely in view, researchers should proceed with open-mindedness and calculated optimism that, when it comes to seeking clues about healthy human longevity, dogs again can deliver. Clearly, when it comes to how dogs might promote healthy human aging, scientific thinking has come a long way from injecting people with extracts of dog testicles—Brown-Séguard's organotherapy of the last century (Borell 1976)—to harnessing pet dogs for serious systematic study of the biology behind successful aging (Figure 1).

Why Dogs, Why Now

At the time of publication of the previous *ILAR Journal* issue on *Animal Models of Aging Research*, flies, worms, and mice were the hardest-working model systems in such studies (Sprott and Ramirez 1997), and their popularity remains high. But a transformational change in thinking has sparked renewed interest in alternative model systems in the field of aging. More scientists are turning their attention to the goal of *healthspan*—healthy longevity, not just the addition of years of life—and are looking for fresh approaches. Can dogs deliver?

Much evidence suggests that they can. In dogs it is possible to accurately measure an array of phenotypes—such as cardiac contractility, the ability to climb stairs, the ability to interact with people—relevant to healthy human longevity, information that is difficult to duplicate in the conventional workhorses of aging research. Furthermore, there is a wealth of canine medical data generated by practicing veterinarians throughout the United States, including clinical and biochemical assessment of specific organ function, medical imaging, and pathology. In short, as with people, researchers know what healthy and sick dogs look like.

Table 1 summarizes the vast array of phenotypic domains relevant to human healthspan that can be assessed in dogs and that serve as the foundation for the development of a standardized, age-sensitive assessment of canine health. For some variables, such as T cell function, red blood cell mass, and kidney function, age-related decline is well characterized; in other instances, such as breed-specific differences in xenobiotic metabolism, the exciting groundwork is being laid (Fleischer et al. 2008). Clearly, generating a complete array of age-specific data from the more than 350 canine breeds would be a laborious and time-consuming undertaking.

A Advertisement, *New York Therapeutic Review*, 1893

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Dogs' lives may offer answers

Doctor goes on 'Old Grey Muzzle tour' to find tricks to longevity, cancer-free living

Figure 1 Evolution of thinking about how dogs might promote human longevity. (A) More than 100 years ago, Brown-Séguard turned to dogs and other animals as a source of testicular tissue for his organotherapy treatment regimen, injections of animal tissue extracts that were touted for their rejuvenating effects on older persons (Borell 1976; reprinted with permission from Johns Hopkins University Press). (B) In 2010, researchers are harnessing pet dogs as a unique field laboratory to better understand the genetic and nongenetic determinants of human healthspan.

It is therefore important to identify a "short list" of breeds that may be particularly instructive, either because they are "typical" or because their longevity suggests that the breed represents an informative outlier compared to other size-matched breeds.

Breed structure and advances in probing the canine genome now make it feasible to pursue hypotheses about genetic influences on longevity by comparing short-lived versus long-lived breeds (see the section below on Genomic Correlates of Successful Aging Phenotypes). Some studies of between-breed differences, such as Speakman's testing of the rate of aging hypothesis, have already yielded interesting results (Speakman et al. 2004).

Table 1 Phenotypic domains relevant to human healthspan that can be assessed in dogs

Domain	Parameter ^a	Key references
Cardiovascular function	Myocardial function, valvular sufficiency, arrhythmia, arterial blood pressure	Strasser et al. 1997
Sensory function	Visual activity, cataract formation, hearing	Tobias et al. 1998
Cognitive function	Learning, memory, affect, social interaction with humans	Cotman and Head 2008; Su et al. 2005
Neuromuscular-skeletal function	Mobility, balance, proprioception, bone density, muscle mass, force plate gait analysis, nerve conduction	
Urologic function	Renal function, glomerular integrity (proteinuria), urinary continence	Pomeroy and Robertson 2004
Reproductive function	Fertility	
Metabolic function	Body composition, insulin/glucose metabolism	Kealy et al. 2002; Larson et al. 2003
Endocrine function	Basal and postchallenge thyroid and adrenal status	Rothuizen et al. 1993
Immune function	Immune cell number and function, response to vaccination, recurrent infection, autoimmunity	Day 2010; Greeley et al. 1996; HogenEsch and Thompson 2010
Cancer resistance	Tumor incidence, age at onset, biological aggressiveness	Waters and Wildasin 2006
Stress resistance	Vulnerability and response to environmental, endogenous stressors; telomere length	McKevitt et al. 2002
Repair capacity	Wound healing, DNA repair, replicative potential of fibroblasts	Li et al. 1996

^aThese parameters can be assessed longitudinally in nonterminal studies. For many of these clinical parameters, postmortem examination of tissues provides informative pathologic correlates.

Studying the determinants of healthy lifespan in populations of pet dogs living in the same environment as humans offers unique, scientifically appealing opportunities. Compared to laboratory-confined model systems, individuals studied under less artificial conditions encounter environmental triggers—pathogens, pollutants—at dose ranges and frequencies relevant to human health. And the compressed lifespan of dogs relative to humans provides an opportunity to apply a life-course perspective to the study of healthspan. Biogerontologists don't want to confine their studies to old animals or old people because the origins of many adult health outcomes are shaped significantly by early life events (Waters 2007). For example, the risk for older people to suffer pathological bone fractures secondary to osteoporosis is strongly dependent on the physiological reserve (i.e., peak bone mass) established in the second and third decades of life. Research on healthy longevity must seek to identify early life events that significantly influence health outcomes; factors implicated by previous studies include early-life growth rate in rodents (Miller et al. 2002), early removal of endogenous sex hormones in dogs (Cooley et al. 2002), and in humans adverse psychosocial events during childhood (Felliti et al. 1998).

Finally, the relatively compressed lifespan of dogs is well suited for intervention trials to evaluate the impact of lifestyle decisions such as diet or dietary supplements, or of

genetic polymorphisms. Pet dogs can provide a testing ground for clinically relevant, healthspan-promoting interventions, fostering a much needed *vertical integration* that builds on the best science from invertebrate and rodent models (Figure 2).

Research Approaches: Six Illustrative Examples of Utility

One of the objectives of this article is to benchmark research progress in dogs and to direct attention to fruitful areas for future research. Table 2 shows some of the research approaches in which dogs can be effective models to address issues relevant to human healthspan. The following sections provide an illustrative example for each approach.

Defining Key Mechanisms of Longevity (Example: The Female Survival Advantage)

Female survival advantage is well documented in certain mammalian species, most notably humans (Austad 2006), where it translates into a greater likelihood that women will live to 100 years, outnumbering men by approximately 4:1 (Terry et al. 2008). Transplantation of ovaries from young mice into ovariectomized female mice increased life expectancy

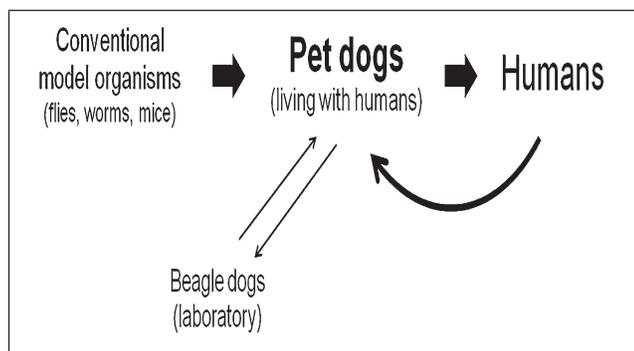


Figure 2 Pet dogs are well suited for mammalian validation of hypotheses generated in invertebrate models. As pet dogs assume a more central role in aging research, it is likely that investigators will conduct fewer studies using laboratory-confined beagles. Pet dogs can provide study populations enriched for disadvantaged individuals (i.e., unfavorable risk factors or health trajectories) that are candidates for healthspan-promoting intervention studies. Also, particular breeds or groups of dogs that demonstrate successful aging in particular domains (e.g., cognitive aging) may be suitable targets for genetic or biomarker studies. The *humans-to-pet dogs* loop depicted here predicts that questions generated by human studies will flow back to pet dogs for further refinement, such as reconfiguring the dose or life-course window (i.e., timing) needed to optimize a particular health-promoting intervention.

proportional to the age of the recipient (Cargill et al. 2003; Mason et al. 2009). But the mouse, biogerontology’s most trusted mammalian workhorse, is not a particularly trustworthy mimic of the sex differences in human longevity because male mice often outlive their female counterparts (Austad 2006; Turturro et al. 2002).

Whether ovary removal early in life can reset longevity parameters in humans has not been evaluated because few young women undergo ovariectomy. In contrast, a large percentage of female pet dogs undergo ovariectomy through spaying at different ages throughout the life course, creating a research opportunity to study the dose response between endogenous ovarian function and longevity. Austad (2010) has noted that research on the basic mechanisms of sex dif-

ferences in longevity is surprisingly sparse and concluded that human sex differences in longevity may be the single most robust aspect of human biology that scientists do not understand in even the broadest terms.

To address this knowledge gap, my colleagues and I at the Center for Exceptional Longevity Studies of the Gerald P. Murphy Cancer Foundation studied pet dogs to determine whether lifetime duration of ovary exposure was associated with longevity. In 2006, a database was established at the Center to track the oldest-living pet dogs in the United States, representing the first such effort. To date, this canine counterpart of the New England Centenarian Study has collected lifetime medical histories from more than 150 canine “centenarians” of a single breed—Rottweilers that have lived to 13 years of age, which is more than 30% longer than the breed standard and is equivalent to 100 years old for humans (Patronek et al. 1997). We estimate that 1 in every 6,000 Rottweilers alive in the United States meets our criterion for exceptional longevity. For comparison, data for most industrialized nations estimate that 1 in 5,000 humans is a centenarian (Perls 2006).

We compared sex and lifetime ovary exposure in the centenarian Rottweilers in our database to a cohort of Rottweilers with typical longevity (8.0-10.8 years) (Waters et al. 2009). Female dogs were twice as likely as males to achieve exceptional longevity. However, removal of ovaries during the first 4 years of life completely erased the female survival advantage. In female dogs, a strong positive association between ovaries and longevity persisted in multivariate analysis that considered other factors, such as height, body weight, and mother with exceptional longevity. A beneficial effect of ovaries on longevity in females could not be attributed to resistance to a particular disease or major cause of death.

Our results in pet dogs mirror the recent findings from more than 29,000 women in the Nurses’ Health Study (Parker et al. 2009). In that study, women who had elective hysterectomy with ovary sparing had lower overall mortality than those who underwent hysterectomy with ovariectomy. Taken together, the findings from dogs and women support the hypothesis that early-life physiological influences, such

Table 2 Research approaches in dogs suitable for addressing issues relevant to human healthspan

Category	Example
Defining mechanisms of longevity control	Ovaries ^a ; rate of living (Speakman et al. 2004)
Intervention studies to compress morbidity and enhance healthspan	Cognitive aging ^a ; gene therapy for renal dysfunction (Brown et al. 2009)
Genomic correlates of successful aging phenotypes	IGF-1 ^a ; candidate loci (Canterberry et al. 2005; Mateescu et al. 2008)
Understanding heterogeneity in disease resistance	Survivors/delayers/escapers in centenarians ^a ; cancer resistance in oldest-old ^a
Noninvasive biomarkers that reveal information on aged target organs	Oxidative stress challenge of blood cells ^a ; osteoarthritis markers (Qi and Changlin 2007)
Revisiting hypotheses originating from human observations	Inflammation and obesity ^a

^aExamples are developed in the text.

as ovarian hormones, lay the foundation for adult health outcomes, including longevity.

Future studies in dogs and women are warranted to define specific ovarian longevity factors and to identify ovary-sensitive biological processes that promote healthy longevity. Pet dogs should provide a tractable mammalian model with a broad range of lifetime ovary exposure for investigating the mechanisms of how ovaries orchestrate extended longevity in both species.

Intervention Studies to Compress Morbidity and Enhance Healthspan (Example: Abrogating Cognitive Aging)

For more than two decades researchers have devoted considerable effort to developing models of age-associated cognitive decline. In dogs, this line of inquiry has been advanced by Cotman and Head and by Milgram and colleagues, who conclude that the aging beagle provides a spectrum of cognition—from intact to selective losses in specific cognitive domains to a more global dysfunction that mimics the deficits seen in early Alzheimer's disease in humans (Cotman and Head 2008). Extensive pathologic examination has documented significant age-associated loss of neurogenesis (the ability to sprout new neurons) and increased oxidative damage in the brain of aged beagles (Head et al. 2002; Rofina et al. 2004; Siwak-Tapp et al. 2007). Careful development of a series of canine cognitive tasks (reviewed in Cotman and Head 2008), analogous to those used in human neuropsychological testing, uniquely positioned these investigators to conduct intervention studies (Milgram et al. 2005, 2007).

After baseline cognitive testing, 48 elderly beagles were randomized to four cognitively equivalent intervention groups: antioxidant supplementation, behavioral enrichment, both interventions, or control group (Milgram et al. 2005). Antioxidant supplementation led to rapid cognitive improvement within 2 weeks that continued for 2 years, while unsupplemented dogs showed progressive decline. In contrast, a cohort of young dogs that received an antioxidant-fortified diet showed no effect on cognition. Elderly dogs that received behavioral enrichment had more accurate learning ability (discrimination learning) that persisted for 2 years. Pathologic examination showed that antioxidant- or behaviorally enriched dogs had significantly less oxidative damage to protein and less neuronal loss in the dentate gyrus, a region of the brain important for visuospatial learning and memory. Taken together, these results point to a pair of long-term interventions—antioxidant supplementation and behavioral enrichment—that may slow age-associated cognitive decline.

Because significant cognitive decline and neuropathology occur in dogs within years rather than decades as in humans, these elegant studies in laboratory-confined beagles have set the stage for pet dog studies that may be particularly useful for longitudinal assessment of cognitive aging. Research in aging pet dogs could help to further define the impact of

lifestyle decisions and environmental factors (e.g., diet, lifetime duration of endogenous estrogen exposure) on age-associated cognitive decline. Moreover, breed-specific responses might provoke intriguing new hypotheses.

Genomic Correlates of Successful Aging Phenotypes (Example: Breed Differences in IGF-1 Haplotype)

Extensive genomic resources, including a high-quality genome sequence (Lindblad-Toh et al. 2005), make the dog uniquely useful for studying the genetic basis for complex phenotypes (Wayne and Ostrander 2007). Because modern breeds represent closed gene pools with a remarkable genotypic and phenotypic diversity (e.g., in disease risk), pet dogs are ideally suited for genomewide association studies for the discovery of genes underlying breed-specific characteristics. Studies have identified canine disease genes for endocrine, ophthalmologic, neurological, and skeletal disorders as well as cancer (Wayne and Ostrander 2007), and have uncovered unique molecular mechanisms, such as dodecamer repeat expansion in epilepsy of wirehaired miniature dachshunds (Lohi et al. 2005).

The growth hormone–insulinlike growth factor (IGF) axis is an evolutionarily conserved pathway linked to longevity in virtually all model systems (Piper et al. 2008). In humans, a mutation associated with decreased IGF receptor activity is overrepresented in female centenarians (Suh et al. 2008). Sutter and colleagues (2007) found a single nucleotide polymorphism haplotype of the gene encoding IGF-1 that is common to all small dog breeds but rare in giant dog breeds. This study demonstrates the use of across-breed genomic scanning in dogs to identify variants responsible for complex traits. Taken together, the recent advances in canine genomic technology boost confidence that dogs can help reveal genes key to healthy longevity. Particularly exciting is the prospect of using the rapidly maturing field of canine genomics to study how gene-environment interactions influence the aging process in the context of environmental triggers shared by humans.

Perhaps the biggest limitation to using dogs in genomic studies relates to the careful selection and quantitation of phenotypes, a problem well recognized in human genetic epidemiologic studies (Fallin and Matteini 2009). In dogs and humans, a high priority should be placed on developing useful *endophenotypes*—measurable intermediate phenotypes, such as insulin resistance or markers of inflammation, that are more proximal to the effects of genetic variation on aging and disease susceptibility. For example, the “yes” or “no” dichotomized binning of continuous traits should be replaced by assessments that more precisely capture the continuum of health and disease. Progress in this arena could yield big dividends because the pathways from gene action to endophenotype are likely to be more recognizable than the complex paths from gene action to an end-stage phenotype, such as disease diagnosis (Reitz and Mayeux 2009).

The Role of Heterogeneity in Disease Resistance (Example: Morbidity Profiles in Centenarians)

Fries (1980) has pointed to postponement of age-associated acceleration of organ reserve loss—so-called compression of morbidity—as a way to increase healthspan (Fries and Crapo 1981). This line of thinking requires fundamental research to identify interindividual heterogeneity and to exploit the plasticity inherent in this decline. Studies in human centenarians have documented considerable heterogeneity in the physical functioning of men and women (Franceschi et al. 2000b). Perls and colleagues have shown that for most centenarians the onset of major life-threatening diseases is delayed, although there is individual variability in the route to exceptional longevity (Evert et al. 2003). In a study of more than 400 human centenarians, Evert reported three different morbidity profiles: *survivors* (38%), who experience the onset of at least one major disease before the median age at death for the cohort; *delayers* (43%), who are free of major disease until after the cohort's median age at death; and *escapers* (19%), who remain free of all major disease until after they reach 100 years.

Using our database, we have studied the morbidity profiles of 114 canine centenarians and found that nearly 60% of them are *escapers*—members of the most profound category of disease resistance (Waters et al., unpublished data). Many pet owners euthanize their dogs when quality of life is severely diminished, resulting in selective survival of dogs that do not develop major diseases until *after* they achieve exceptional longevity. As a result, compared to extreme-aged humans, canine centenarians represent a more penetrant phenotype of disease resistance, creating a research opportunity to explore the genetic and nongenetic factors that confer disease resistance.

Like humans, Rottweilers are prone to developing cancer. However, we have shown that extremely old Rottweilers, like human centenarians, are resistant to cancer mortality (Cooley et al. 2003; Smith 2006). Autopsy studies in dogs are currently under way to determine the nature of this cancer resistance. In our experience, autopsy frequently reveals clinically undetected cancer burden, in some cases two or more independent cancers. These preliminary findings suggest canine centenarians may provide clues to figuring out what every cancer scientist wants to know: *how to transform cancer from a lethal disease to a nonlethal nuisance*. A better understanding of the aging-cancer connection (Martin 2009) will be a highly instructive step toward thinking about new ways of compressing the morbidity of aging and age-related diseases.

Information from Noninvasive Biomarkers about Organ Microenvironments (Example: Oxidative Stress Challenge of Peripheral Blood Lymphocytes)

Because Westernized human populations are cancer prone, cancer resistance may be considered a phenotype of successful

aging. There is great need for individualized risk prediction that can identify people with unfavorable health trajectories, including high lifetime risk for cancer, as they represent candidates best suited for health-promoting risk modification. For example, the inability to segregate men into high- versus low-risk groups for developing prostate cancer led to the enrollment of more than 32,000 subjects to test a single hypothesis: whether daily supplementation with the antioxidants vitamin E or selenium can reduce cancer incidence (Lippman et al. 2009).

Like men, dogs develop spontaneous prostate cancer and thus provide an animal model to assess risk (Waters et al. 1996, 1998). Oxidative stress drives the accumulation of DNA damage in the aging prostate and other tissues and thereby contributes to cancer development (Malins et al. 2001). We reasoned that if oxidative stress plays an important role in prostatic carcinogenesis, then evaluating the sensitivity of peripheral blood lymphocytes (PBLs) to oxidative stress challenge might provide a simple test to noninvasively predict genomic damage in the prostate.

We tested this hypothesis in a population of 69 elderly male beagles after they had completed a randomized feeding trial to achieve the broad range of dietary selenium status observed in US men (Waters et al. 2007). Alkaline Comet assay was used to directly compare the extent of DNA damage in PBLs with prostatic DNA damage in each dog. We found that sensitivity of PBLs to oxidative stress challenge with hydrogen peroxide predicted dogs in the highest tertile of prostatic DNA damage; dogs with PBLs highly sensitive to hydrogen peroxide were more than 7 times more likely to have high prostatic DNA damage than those in the peroxide-resistant group. This risk stratification was observed in multivariate analysis that considered other factors that might influence DNA damage.

Our findings in dogs parallel those from men (Lockett et al. 2006) showing that PBL sensitivity to hydrogen peroxide challenge, but not endogenous PBL damage, can serve as a noninvasive predictor of prostatic DNA damage. The ability of alkaline Comet assay to detect heterogeneity in the response of PBLs to oxidative stress challenge may be a powerful tool to detect interindividual differences in latent genetic instability. The implications of this work extend far beyond the prostate, as we have also demonstrated the utility of this challenge to identify individual dogs that have the highest DNA damage in the brain (Waters et al., unpublished data).

Revisiting Human-Based Hypotheses (Example: The Association Between Inflammation, Obesity, and Aging)

A decade ago, Franceschi coined the term “inflammaging” to describe the apparent proinflammatory state of elderly humans (Franceschi et al. 2000a). Since then, numerous studies have documented elevated levels of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha, in older adults, fueling the hypothesis that aging is innately proinflammatory (Danesh et al. 2008). However, other investigators have challenged whether increased inflammation is an obligate phenotype, positing that

the proinflammatory state of the elderly may reflect an accumulation of lifestyle factors, particularly obesity, or the high incidence of atherosclerosis and other comorbid diseases (Ferrucci et al. 2005). The relationship between energy balance, obesity, and inflammation, and their collective impact on healthy longevity, are topics of intense interest (Finch 2007; Speakman et al. 2008). Studies in rodents undergoing surgical extirpation of visceral fat deposits suggest that visceral adipose tissue modulates longevity (Muzumdar et al. 2008) and show that the removal of visceral but not subcutaneous fat exerts favorable effects on endophenotypes such as insulin sensitivity (Gabriely et al. 2002).

In dogs, diverse age-related changes in immune function have been well characterized. Aging dogs, like humans, experience an immunosenescence characterized by predictable alterations in T cell subsets and functional deterioration of natural killer (NK) cell function (Day 2010; Greeley et al. 1996). An overt proinflammatory state in elderly dogs, however, has not been reported.

Estimates indicate that 20-40% of the pet dog population is clinically obese (Courcier et al. 2010; Hand et al. 1989). Obese pet dogs subjected to a weight loss intervention (i.e., reduced calories, increased exercise) had significantly lower plasma levels of the inflammatory markers TNF-alpha and C-reactive protein (German et al. 2009). In another study, gene expression profile data from young adult (1-year-old) and geriatric (12-year-old) beagles suggested an age-associated increase in inflammatory activity in canine adipose tissue (Swanson et al. 2009), findings that mimic those from studies of adipose tissue of mice (Wu et al. 2007). Thus pet dogs appear to be well suited for further testing of the inflammaging hypothesis. In fact, conducting such studies in a relatively atherosclerosis-free species, like dogs, might provide a valuable opportunity to tease out aging-related effects from the contributions of comorbid disease.

Conclusion

Our work has championed the idea of harnessing pet dogs as one of biogerontology's new workhorses. It is time to travel beyond the physiological familiarity of the laboratory beagle to explore a new paradigm: the informative, virtual field laboratory of pet dogs. This represents a different kind of field work: not sporadically making observations of animals living in the wild but instead tracking individuals with an intensity of medical surveillance that is rivaled only by the medical care their owners receive.

By creating a nationwide database to study exceptional longevity in pet dogs, investigators at the Murphy Cancer Foundation's Center for Exceptional Longevity Studies have taken an important first step toward assessing the utility of pet dogs for testing hypotheses relevant to human healthspan. This research has already led to some provocative findings related to sex differences in longevity, heterogeneity of disease resistance, and the aging-cancer connection.

Yet the potential of this research approach remains largely untapped. Future lines of inquiry that are particularly promising include (1) the generation and testing of hypotheses related to basic biology by capitalizing on robust breed-specific differences in canine longevity (Patronek et al. 1997); and (2) hypothesis-generating cross-sectional and longitudinal observational studies as well as scientifically rigorous intervention trials.

"Science is not meant to cure us of mystery, but to reinvent and reinvigorate it," wrote Robert Sapolsky (1994, ix). Scientifically grounded and much more potent than the infamous extracts of Brown-Séguard, the pet dog paradigm proffered here enlists dogs as an invigorating force—introducing fresh research opportunities, forging new paths, enabling new ways of seeing.

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