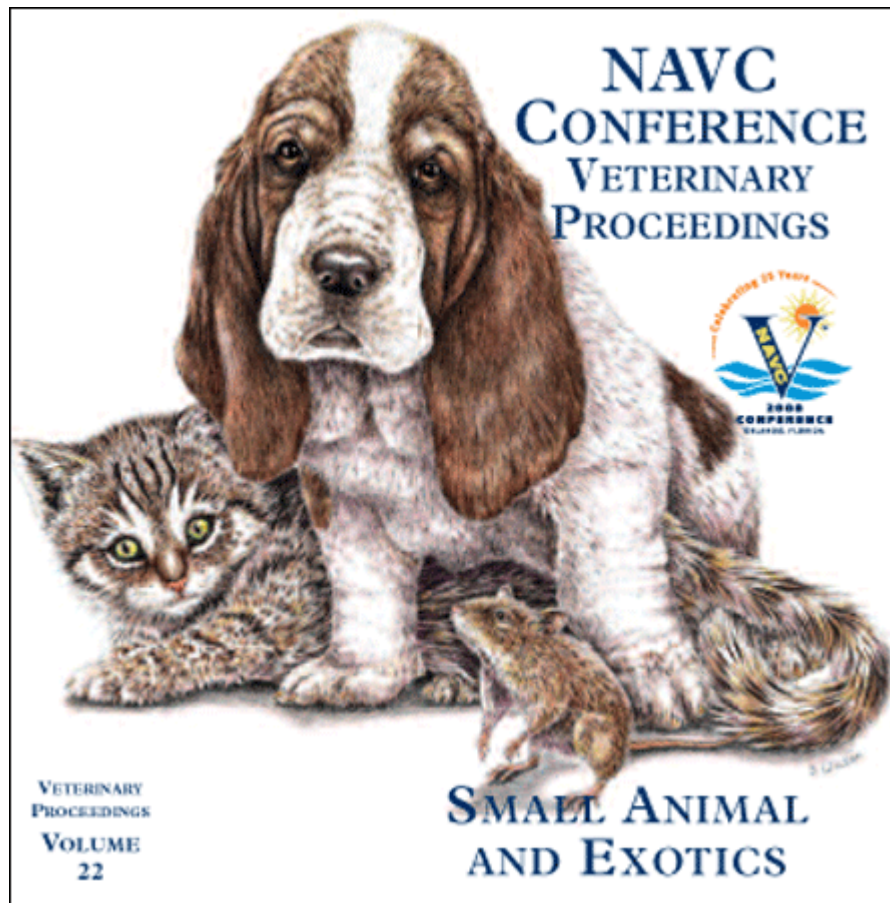# Proceeding of the NAVC
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AGING WELL: HOW THE SCIENCE OF AGING INFORMS THE PRACTICE OF WELLNESS

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Why do we age? What are the genetic and non-genetic determinants of exception longevity? If cancer is indeed the product of time-related accumulation of genetic damage, then why are the oldest-old cancer resistant? The goal of this article is to illustrate how investigative efforts to answer these and other questions relevant to the biology of aging will eventually provide clinicians with best practice guidelines to promote healthy longevity.

UNDERSTANDING THE AGING PROCESS

Not all organisms undergo senescence at the same tempo. Dogs and humans exhibit gradual senescence (deterioration over years to decades), whereas other species, such as bamboo, have very rapid senescence (deterioration over days). There is an eclectic group of organisms that exhibit negligible senescence; age-related deteriorative changes are virtually imperceptible in these species. Not surprisingly, organisms with negligible senescence, including rockfish and bristlecone pine, are currently the subject of great scientific interest.

Understanding the mechanisms of organismal senescence and how morbidity can be compressed, culminating in an extension of healthy life span, is the goal embraced by most biogerontologists. It is important that these aims be clearly articulated to the public. It is also critical that the public understands what are not the goals of biogerontology research. For example, reversal of aging and achieving immortality are not considered tenable objectives.

Lessons From Evolutionary Biology

It has been argued that longevity—not aging or senescence per se—is under genetic control. These so-called longevity genes extend longevity by increasing physiological reserve or increasing disease resistance, rather than having a direct effect on the intrinsic rate of aging. Evolutionary biologists would concur that genes, which regulate late-life deterioration, would not be under the influence of natural selection. Instead, natural selection favors genes that influence the likelihood of reproductive success, because organisms rely upon the successful completion of development and reproduction to perpetuate the species. During the post-reproductive period, however, the force of natural selection quickly diminishes, rendering organisms ill equipped to protect themselves against the age-related accumulation of molecular damage. Seldom is this an important consequence to animals living in the wild, because in general, they experience relatively brief post-reproductive life spans owing to their vulnerability to predators, accidents, or infectious diseases. In contrast, dogs, humans, and other highly protected domesticated animal populations do encounter the manifestations of organismal senescence, including the development of cancer and other age-related degenerative diseases.

When it comes to age-related deterioration and disability, at least two tenets of evolutionary theory would suggest that humans, dogs and other domesticated species are indeed hard-wired for post-reproductive calamity. First, the Disposal Soma Hypothesis states that after reproduction, the soma (body) can be thrown away. Second, genes that confer an advantage early in life may also exert detrimental effects in the post-reproductive period—the Theory of Antagonistic Pleiotropy. The incidence of several age-related diseases is likely to be under the control of such antagonistically pleiotropic genes. For example, genes that stimulate abundant blood vessel formation within the placenta (favoring successful reproduction early in life) might be considered detrimental later in life because they would promote a rich supply of blood vessels to rapidly growing tumors. Moreover, it is expected that the frequency of alleles that exert these late life detrimental effects would be maintained or even increased in the population, owing to their early-life benefit.

In his famous treatise, "An Unsolved Problem of Biology," Nobel laureate Sir Peter Medawar noted that in order to understand the consequences of senescence and age-related diseases, one would have to study the aging process of "protected" species. In a classic thought experiment, in which Medawar considered the aging of glass test tubes, he pointed out that in order to observe the consequences of aging, test tubes would have to be "domesticated"—that is, kept sheltered from damage in a little box so they would not suffer early "death" by rolling off of the laboratory bench.

Thus, organismal senescence and accompanying age-related diseases is an inevitable by-product of domestication. An organism is not built with any regard for optimizing aging. Instead, an organism is designed to successfully and advantageously complete its maturation and reproduction. As a consequence, one expects to see an accumulation of molecular disorder in species, which attain a prolonged post-reproductive life span. This progressive increase in molecular disorder leads to organismal senescence—physiological deterioration, an increased risk for age-related diseases, and an increased mortality rate.

Lessons From Studying the Oldest-Old

Centenarians—people who live to be 100 years—provide a potentially valuable "natural experiment" of highly successful aging. To date, the search for specific environmental exposures or lifestyle factors (eg. diet, education, physical activity) that confer an increased likelihood of living to 100 years has not been fruitful. Among centenarians, females outnumber males by more than 2:1. Among women, successful late reproduction—live childbirth at 40+ years—is a strong predictor of exceptional longevity. Larger particle size of high and low-density lipoproteins and higher plasma antioxidant

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capacity have also been associated with exceptional longevity in humans.

Siblings of centenarians are 15 times more likely to live to 100 years compared with the general population. The sustained mortality advantage seen in siblings of centenarians is observed throughout the life course, suggesting that their good fortune may be more strongly influenced by genetic than by environmental factors. A few genes in humans have already been implicated as candidate "longevity enabling genes" because the "bad" polymorphic variants of these genes are underrepresented in centenarians. These bad variants include the apolipoprotein E∈4 allele and the angiotensin-converting enzyme D allele. Genetic linkage analysis has provided evidence that a gene or several genes on human chromosome 4 significantly contribute to exceptional longevity. It should be noted that the genetic factors that contribute to exceptional longevity might be different from the genetic determinants of *average* life span.

Centenarians outlive the lot of us, but just how healthy are centenarians? When it comes to vulnerability to major age-related diseases, a recent study of lifetime medical histories suggests there are three flavors of centenarians: (1) SURVIVORS—those individuals with onset of at least one major disease prior to 80 years of age; (2) DELAYERS—those individuals who are free of all major diseases until after 80 years of age; and (3) ESCAPERS—those individuals who are free of all major diseases until after 100 years of age. This important study confirmed that centenarians are indeed a highly heterogeneous population—38% SURVIVORS, 43% DELAYERS, and 19% ESCAPERS. However, one can conclude that significant disease resistance is a characteristic of many centenarians; in fact, more than 60% of centenarians remained free of all major diseases until after the median age at death for their birth cohort. Our analysis of exceptional longevity in pet dogs reached a similar conclusion—76% of the oldest-old dogs delayed the onset of major diseases, and more than half of extreme aged dogs had profound disease resistance (ie, ESCAPERS). Interestingly, men and women may follow different trajectories to achieve exceptional longevity—male centenarians are less heterogeneous and healthier than female centenarians are.

Undoubtedly, exceptional longevity is a complex trait reflecting genetic, environmental, and stochastic (chance) influences. Based upon our current understanding of extreme aged humans and pet dogs, we posited that disease resistance is the central and essential determinant of exceptional longevity. In the extreme aged, disease resistance may be manifested as disease avoidance, delayed onset of clinical disease, or decreased mortality from specific diseases. High physiologic reserve likely contributes to exceptional longevity, because it may delay the clinical onset of diseases or ameliorate the deleterious effects of co-morbid conditions. Although counterintuitive, it remains unproven whether an individual's intrinsic rate of aging is a significant determinant of exceptional longevity. To date, there are no definitive data from dogs or humans supporting the hypothesis that a slow rate of physiologic decline is essential to achieving exceptional longevity. Future studies that collect longitudinal data on an array of age-sensitive physiologic parameters (eg, muscle strength, cardiovascular compliance, neurologic processing, inflammation/immune response) are needed to determine whether individuals reaching extreme age demonstrate a significantly different rate of physiologic decline than individuals with usual longevity. The compressed life span of dogs compared with humans could make such studies feasible in pet dogs.

THE COMPLEX RELATIONSHIP BETWEEN AGING AND CANCER

The association between aging and cancer is compelling enough for one author to formally consider gerontology as oncology. Conceptually, the association between aging and cancer can be dichotomized into: (1) the influence of aging on cancer risk; and (2) the influence of aging on the biological behavior of resultant cancers.

In humans, the risk for most adult-onset cancers increases dramatically with increasing age. For 12 major human cancers, more than 50% of cases are diagnosed in elderly individuals over 65 years of age. Experimental evidence also supports the hypothesis that a host's susceptibility to develop cancer is age-dependent. In an important study by McCullough and colleagues, young (3- to 9-month-old) and old (18- to 24-month-old) rats received implantation of cancerous rat epithelial cells into their liver. On day 7 after tumor cell implantation, the incidence of tumors in both young and old rats was 100%. However, on day 85 post implantation, all of the tumors had regressed in young rats, while tumors were present in 17 of 19 (89%) old rats. The striking age-dependent regression of experimental liver tumors in this study clearly demonstrates that an old host provides an environment that is in some way better suited for the survival and proliferation of tumor cells.

A recent study of transgenic mice suggests a previously unexpected relationship between cancer risk and aging. Mice over expressing the tumor suppressor gene, p53, showed profound tumor resistance, but protection against tumors was *not* associated with increased longevity. Unexpectedly, these mice had shorter lives than wild type mice because they had earlier onset of age-related deteriorative changes (eg, diminished muscle mass, dermal thinning, scoliosis). These results are consistent with the hypothesis that tumor suppression in mammals comes at a cost—an accelerated rate of aging.

Data from humans and dogs suggest that host age may influence the biological behavior of malignant tumors. It has been observed that certain tumors behave more aggressively in young adults, in contrast to the more indolent clinical course of these tumors in elderly hosts. For example, more than 50% of stomach cancers in young people (30—39 years old) are poorly differentiated (poor prognosis), whereas fewer than 5% of stomach cancers affecting people over 85 years of

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age are poorly differentiated. Our data show that the youngest dogs that develop prostate cancer are almost 7 times more likely to have skeletal metastases at the time of prostate cancer diagnosis than the oldest dogs that develop the disease.

Although cancer is a disease strongly associated with aging, age-specific cancer mortality rate in humans actually *declines* in the tenth decade of life. Indeed, scientists who study centenarians have uncovered a puzzling paradox—the oldest-old humans seldom develop lethal cancers. Studies in our laboratory suggest a similar decline in the percentage of extreme aged dogs that succumb to cancer. Taken together, this raises the possibility that cancer resistance genes are overrepresented in the oldest-old, where they may influence longevity by protecting old tissues from the development of life-threatening malignant tumors. At present, the precise nature of the apparent cancer resistance in the oldest-old is poorly defined at the tissue level, because few autopsy studies have been performed.

APPLYING A LIFE COURSE PERSPECTIVE TO AGING AND WELLNESS

It makes good sense to apply a life course perspective to studying the determinants of life span. Biogerontology should not be confined to the study of old cells, old dogs, or old people. The origins of many adult health outcomes are shaped significantly by early life events and experiences. For example, the risk of older people to suffer pathologic bone fractures secondary to osteoporosis is strongly dependent upon the peak bone mass established in the second and third decades of life. Similarly, we have shown that Rottweilers that undergo ovariohysterectomy or castration before 12 months of age have a 2- to 3-fold greater risk of developing osteosarcoma as adults compared with dogs that remain sexually intact throughout their lifetime.

Clearly, there are many unresolved questions relevant to the question of why do we age. Today, it is imperative that veterinarians and other scientists take an active role in shaping public dialogue on the goals of aging research—the compression of morbidity and extension of healthy life span.

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