Why do we age? What are the genetic and nongenetic determinants of highly successful aging? If cancer is the product of time-related accumulation of genetic damage, then why are the oldest-old people and dogs resistant to cancer? Substantial research progress is deepening our understanding of the aging process, leading clinicians and pet owners toward best practice guidelines, including the nutritional interventions and lifestyle decisions that will promote healthy longevity.

SUCCESSFUL AGING: MORE THAN GENES
Whether genes influence life span is not subject to debate, as no amount of environmental protection or enrichment can produce a rat that lives as long as the average German Shepherd. Scientists have identified specific genes that regulate life span in worms, flies, and mice. What remains up for grabs is whether any of these genes actually prolong life span by slowing down the rate of aging. Scientists are still undecided whether those of us who live the longest actually have a slower rate of aging than people with usual longevity, or whether the difference is in genes that regulate disease resistance.

Data from human twin studies suggest that only 25% to 30% of the variation in life span among individuals can be attributed to genetic factors. In other words, there is considerable plasticity to longevity. This means that lifestyle decisions are important. Now, scientists are focusing on what factors in the external environment (e.g., diet, exposure to chemicals) or the internal environment (e.g., hormones, oxidative stress) significantly influence an individual’s life span. There is no doubt that nutrition can have a profound influence on physiology and disease. With more research, we are positioning ourselves to understand how optimizing nutrition can promote successful aging.

THE GOAL OF SUCCESSFUL AGING
Helping our pets to age more successfully is one of the prime goals of every veterinary health team. What is successful aging, and how is it measured? Successful aging means retaining robustness in physical and sensory function amidst age-related decline. It manifests itself at the biochemical and clinical level as physiological resilience—the ability to mount an effective, context-appropriate response to challenge. Clinical examples include the healing response to bone fracture, immune response to viral infection, or the ability to restore normal serum creatinine after exposure to a nephrotoxic insult. Disease resistance is also an essential determinant of highly successful aging—a lesson scientists have learned from studying dogs and humans who reach exceptional longevity. Successful aging translates into not only living longer, but living longer; healthier lives. Healthy longevity—also called healthspan—is the prize for which scientists, clinicians, and pet owners should commit themselves. Creating successful aging trajectories through early superior life choices and interventions throughout the life course that favor disease resistance (rather than just focusing our anti-aging efforts on geriatric pets) will undoubtedly yield greater dividends.

UNDERSTANDING THE AGING–CANCER CONNECTION
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 individuals older than 65 years. Similarly, in dogs the incidence of cancer rises dramatically with increasing 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 months of age) and old (18 to 24 months of age) rats had cancerous rat epithelial cells implanted 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, whereas tumors were still present in almost 90% of 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. We believe that to move closer to the goal of cancer prevention, it will be essential to learn more about old tissues because most cancers develop there.

**SUCCESSFUL AGING TRANSLATES INTO NOT ONLY LIVING LONGER, BUT LIVING LONGER, HEALTHIER LIVES. HEALTHY LONGEVITY—ALSO CALLED HEALTHSPAN—IS THE PRIZE FOR WHICH SCIENTISTS, CLINICIANS, AND PET OWNERS SHOULD COMMIT THEMSELVES.**

Possible health trade-offs are an important consideration that complicates decision making. A study of transgenic mice suggests a previously unexpected relationship between cancer risk and aging.

Mice over-expressing the p53 tumor suppressor gene showed profound tumor resistance, but protection against tumors was not associated with increased longevity. Despite their avoidance of cancer, these mice had shorter lives than wild-type mice because they had earlier onset of age-related deteriorative changes (e.g., diminished muscle mass, dermal thinning, scoliosis). These results are consistent with the hypothesis that tumor suppression in mammals comes at a cost—that cost is accelerated aging.

Data from humans and dogs suggest that 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 people 30 to 39 years of age are poorly differentiated and carry a poor prognosis. In contrast, fewer than 5% of stomach cancers affecting people older than 85 years are poorly differentiated. Our data show that the youngest dogs that develop prostate cancer are almost 7x more likely to have skeletal metastases at the time of cancer diagnosis than the oldest dogs that develop the disease. A mechanistic explanation for the young host–aggressive cancer connection awaits further exploration.

Although cancer is a disease strongly associated with aging, the age-specific cancer mortality rate in humans actually declines in the 10th decade of life. In fact, scientists who study centenarians have uncovered a puzzling paradox: The oldest-old humans seldom develop lethal cancers. Data from our Exceptional Longevity Data Base suggest a similar decline in the percentage of extreme-aged dogs that succumb to cancer.

Taken together, these findings raise 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. The precise nature of this apparent cancer resistance is poorly defined, so we are performing autopsy studies in oldest-old dogs in an attempt to deepen our understanding.

**GATHERING CLUES TO SUCCESSFUL AGING: LESSONS FROM STUDYING THE OLDEST-OLD**

In 2005, we established The Center for Exceptional Longevity Studies at the Gerald P. Murphy Cancer Foundation. The aim was to test a new idea—that the secrets to successful aging can be revealed by studying exceptional longevity in pet dogs. To accomplish this, we set out to conduct the first systematic study of the oldest-old dogs, starting with Rottweilers. We created The Exceptional Longevity Data Base (ELDABA)—the world’s first collection of medical history and lifestyle information on canine centenarians. This work has already led to important discoveries. By carefully studying the association between the number of years of lifetime ovary exposure and longevity in female Rottweilers, we discovered that keeping ovaries longer is associated with living longer. Our work pointed to a new line of thinking: Ovaries are part of a system that promotes longevity.

This transformational way of thinking—seeing ovaries not just as reproductive units but as healthspan-promoting endocrine organs—is also supported by emerging research on the longevity-extending effects of ovaries in women and mice.

**THE UNIQUENESS OF THIS RESEARCH APPROACH**

As the leader of the first study of the oldest-living pet dogs in the United States, I have studied in their homes more than 70 exceptionally long-lived Rottweilers who have reached the age of 13—equivalent to 100-year-old people (Figures 1 and 2). Using this out-of-the-laboratory-and-into-the-living-room approach, I am making first-hand observations on these exceptional dogs, which is leading to new ways of thinking about what it takes to age successfully. This includes new ways of thinking about how to fight off lethal cancers, on the relationship between stress and aging, and factors that influence lifetime cruciate ligament survival.

We are getting a unique, privileged view of a successfully aging population. No surprise that this work is re-shaping our perspective on the factors that feed highly successful aging. This essential fieldwork is analogous to the approach used by scientists who make their way into the jungle to try to figure out what it means to be “gorilla.” The only difference is that we are venturing out to figure out what it means to age successfully. The challenge is to enter each living room with a brute open-mindedness—attempting to see fresh clues that completely
violate my previous training, my preconceived notions of aging. This is because our ability to make real progress—to shake loose from the tyranny of old ideas—will depend on our ability to uncover the most reliable clues. This will demand linguistic readiness—a willingness to develop and use new language that will better capture the scope of our research questions and more accurately map our progress in answering them.*

REFERENCES


* The notion that the scientific method is limited by language is addressed in my recent TEDx Purdue talk titled “The Oldest Dogs as Our Greatest Teachers: Get the Words Out of Your Eyes,” which is available on YouTube.