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Declining Physiological Reserves: Defining Aging

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Aging is the sum of the deleterious effects of time upon the cellular function, microanatomy and physiology of each body system. These biological aging changes manifest in progressive deteriorations in physical condition, organ function, mental function, and immune response, but not necessarily correlating with the patient's actual chronological age. How old an organism is in actual time is referred to as "chronological" aging and should be distinguished from "biological" aging," the relative functional age of each of an individual's diverse organ systems. Because there is little correlation between biological and chronological age, each animal must still be evaluated as an individual.

Glossary of Abbreviations
ALP: Akaline Phosophatase
ALT: Alanine Aminotransferase
ATP: Adenosine Triphosphate
BMR: Basal Metabolic Rate
GI: Gastrointestinal
GTT: Gamma Glutamyl Transferase
NH: Nodular Hyperplasia
NSAIDS: Nonsteroidal Anti-Inflammatory Drugs

Aging is not a specific disease, but rather a complex process influenced by genetics, environment, stress and nutrition. These factors affect progressive irreversible degenerative changes of all body tissues. Aging in dogs and cats is associated with gradual and progressive deterioration in the delicate body systems that eventually results in decreased physiological functions.

As the functional organ reserves are gradually lost, the long-term result is a physiological decline of the major organ systems leading to an altered response to stressors, infections and various drugs. At some stage in the progressive decline (these "benchmark tipping points"), all physiological reserves are exhausted resulting in overt changes in diagnostic screening tests, biochemical parameters, and/or the onset of clinical symptoms of age-related disease.

Unfortunately the organ system changes are often subtle or undetected until the patient is stressed by illness, hospitalization, medications or general anesthesia. Increasingly, those changes are routinely identified on senior wellness screening tests further validating the value of such testing protocols.

Although these processes influence one another, physiological decline does occur independent of disease. Age-related changes are further impacted by those diseases commonly seen in elderly patients. Over the past decade, the veterinary profession has attempted to make clear distinctions between the process of aging and various age-related diseases. However, the dichotomy between aging and age-related disease continues to be somewhat ambiguous and blurred.

In biology, senescence is the state or process of aging. After a period of renewal (maintenance years), senescence is characterized by animals' declining physiological reserves that hamper their ability to respond to stress and maintain homeostatic balance, thus resulting in increased susceptibility to disease. The older patient is more likely to have multiple marginal organ system dysfunction and significantly less functional reserve capacity than the younger patient.

The physiological decline and lack of reserves are responsible for the deterioration in physical condition, organ function, sensory function, mental function, and immunity. The rate of the physiological decline and lack of reserves varies among species, breeds and even littermates. Individuals of the same chronological age may experience these alterations differently, i.e., for some, the level of decline may be rapid and dramatic; for others, the changes may be much less significant.

Using the patient's age as a benchmark of collective decline is appropriate. However, because each organ has a different rate of biological aging, any critical assessment of a patient's overall health status should be based on a complete health screening of each specific organ function, if possible.

With the large variability in those age-dependent physiological changes in patients, the only way to be certain about various organ functions is to measure them whenever possible. With the various diagnostic screening tools currently available, the physiological decline can be accurately assessed usually before clinical symptoms appear. Specific aging changes are often identified during a comprehensive history or an age-specific physical examination, or uncovered on a biochemical screening profile or other advanced diagnostic technique. Accurately assessing the degree of physiological decline of each organ system is critical in developing an appropriate senior wellness program, proper nutritional strategies, correct drug selection/dosage, and suitable anesthetic protocol.

The process of aging is complex and based on the widely accepted "theories of aging," initiated by a combination of genetic, biological and/or environmental factors all contribut-

ing to the progressive regression called aging. However, it is the declining physiological reserves that define our medical approach to the geriatric patient.

Decisions regarding specific drug therapies, anesthetic protocols, pain management strategies, and quality of life issues hinge on the variety of declining physiological "benchmarks." A clear understanding of the level of physiological decline of each organ system dictates how a specific patient is best managed.

Assessment of the level of physiological decline in each organ system requires diagnostic evaluations. The interpretation of a patient's urinalysis, hematology and biochemistry panels results in data used to aid in the diagnosis, prognosis and treatment of various conditions. This data combined with appropriate imaging techniques and other advanced diagnostics presumably will facilitate early identification of both physiological decline and various pathological states.

The generalized changes associated with aging include dryness of all tissues, progressive degeneration of organ function, tissue hypoxia, cellular membrane alterations, decreased enzyme systems, decreased immune competence, and definite personality alterations.[1,2]

Thermoregulation

Effective thermoregulation (heating and cooling) is deceased in the aging dog. Their decreased ability to pant and decreased cardiac output combined with ineffective vasodilatation make older pets more prone to heat stroke. Older patients are more susceptible to cold ambient temperatures. This age-related cold intolerance is attributed to decreased basal metabolic rate, decreased cardiac output, and decreases in peripheral vaso-constriction, often combined with less subcutaneous fat in the very old pet.[1] The resulting response to "cool ambient temperatures" may manifest as behavioral issues including hiding, shivering/trembling, sleep-cycle disturbances, and/or a reluctance to go outside for elimination. On a more critical note, the older patient is more susceptible to anesthesia-induced hypothermia, which can produce arrhythmias, decreased coagulation and increased risk of post-operative infections.[3] The inferences are comfort issues and anesthesia risks.

Metabolism

As animals age, their basal metabolic rate (BMR) decreases. The consequences include weight gain if there is not a corresponding decrease in caloric intake.[4,5] With a decreased BMR, less metabolic heat is generated resulting in a "cold intolerant" patient. Another impediment is decreased cell turnover in the gastrointestinal (GI) tract making the patient more susceptible to erosion and ulceration. The inference is weight control.

Integument

The integumentary aging changes are the most obvious to the owner. The hair undergoes some degree of pigment loss (graying), obvious follicular atrophy (coat thinning), plus decreased sebum production (dry, scaly skin and coat).[6] The decrease in both quantity and quality of the sebum makes the skin and coat dry, flaky and dull. The nails become longer, more brittle, and usually thicker as a result of decreased exercise and decreased blood flow to the digits. The skin undergoes dermal epidermal atrophy and may develop areas of hyperkeratosis on the nasal and footpads. The inferences are mainly dietary and cosmetic.

Cardiovascular Decline

Functional reserve is reduced with age due to myocardial fibrosis and free wall thickening. These changes reduce efficiency, ventricular filling and cardiac output.[7] Regional and organ blood flow also decreases.[2,3] To compensate for a decreased cardiac output, older patients primarily increase the stroke volume mainly through increased preload and increased atrial kick.[3] Chronic valvular disease (valvular fibrosis/endocardiosis) resulting in valvular incompetence is the most common heart condition of older dogs.[8] The inference is cardiac disease, dietary, anesthesia, and the potential consequences of decreased blood flow to the brain and kidneys.

Pulmonary Decline

Mechanically the patient loses thoracic compliance, develops progressive atrophy of the diaphragm and intercostals muscles, and loses alveolar elasticity. The result is a decrease in arterial oxygen concentration. While difficult to quantify, it is very important in general anesthesia.

Renal Decline

The renal system has aging structural changes that may not be clinically evident. Uncovering chronic progressive renal disease is often difficult in the very early stages. A loss of 50% of functional nephrons is not unusual in older animals; however, that degree of nephron loss cannot be easily detected.[9] Proper assessment of urinary system function involves an accurate history (estimated water consumption/urine output when possible), a complete physical examination, complete urinalysis, and serum chemistries. Depending on the specific case and initial laboratory findings, microbial cultures and imaging may also be indicated.

There are specific physiological/biochemical benchmarks of the declining physiology associated with the progressive nephron loss. The aging kidneys have a decreased renal blood flow, decreased glomerular filtration rate and decreasing ability to concentrate the urine.[2,10] These physiological benchmarks may be picked up on a biochemical profile (BUN, serum creatinine and serum phosphorous elevations) and urinalysis in the later stages. With the large variability in age-dependent changes in renal function, the only sure way of determining

the animal's renal function is to measure them. However, an age–dependent dosage reduction should be anticipated for all drugs that are eliminated by the kidneys.[11] The inferences are primarily chronic renal dysfunction, dietary, anesthesia, and drug elimination.

Hepatic Decline

Geriatric patients can have a decrease in liver mass of up to 50%, which leads to decreases in liver function and available hepatic enzymes for metabolism and detoxification.[1,2,12] The age-related decreases in cardiac output result in decreased blood flow to the liver with subsequent decreases in coagulation factors, plasma proteins and serum glucose. Fatty infiltration of the hepatocytes and nodular hyperplasia (NH) are the two most common age-related lesions in the canine liver.[13] Each could be causes for the mild elevations in serum alkaline phosphatase (ALP) commonly found in older dogs.

The liver performs a wide variety of different and seemingly unrelated functions. It is important in plasma protein synthesis (including coagulation factors), carbohydrate (glucose) metabolism, lipid metabolism, bilirubin metabolism, BUN formation, bile synthesis, plus detoxification of various substances. Biochemical profiling of the liver entails assessments of the liver enzymes, i.e., serum alanine aminotransferase (ALT), ALP and serum gamma glutamyl transferase (GTT), and the various (indirect/secondary) liver function tests, i.e., BUN, glucose, total protein, cholesterol, and fibrinogen. Often there is no direct correlation between liver function, the degree of enzyme elevation, and the prognosis. Pre/post prandial bile acids are a commonly used liver function test. The early inferences are drug elimination including NSAIDs and dietary selection.

Skeletal Muscle Atrophy

Progressive age-related skeletal muscle atrophy is a common finding in older dogs. It is the result of a generalized decrease in the number of muscle cells, i.e., muscle fiber fibrosis, combined with a decreased sensitivity to adenosine triphosphate (ATP). On physical examination, atrophy of the semimembranosus, semitendenosis biceps femoris and quadriceps is most obvious. The consequences of this muscle atrophy include inactivity and hind limb locomotion issues. The inference is quality of life issues and dietary selection.

Table 1. Prevalence of Sensory Decline in Dogs[16]

• Visual Impairment
– 41% of dogs >12 Years Old
– 68% of dogs > 16 Years Old
• Hearing Impairment
– 48% of dogs >12 Years Old
– 97% of dogs > 16 Years Old

Gastrointestinal Decline

Impaired swallowing, decreased gastrointestinal motility, decreased gastric acid secretions, decreases in digestive enzymes, and decreased absorptive capacity may be found in the older patient.[2,11,14,15] The normal loss of olfactory neurons combined with the loss of taste buds decrease the palatability of most foods. A picky appetite may result.[2] A lack of sufficient saliva to aid in swallowing dry food also can contribute to a deceased appetite in the "healthy" older pet.[1] The inferences are dietary, GI ulcerations and partial inappetence.

Sensory Decline

Decreases in hearing and vision are common age-related problems that increase in frequency with aging (Table 1). Changes in vision and hearing are referred to as sensory dysfunctions and often result in changes in behavior patterns.[16] The inferences are quality of life issues.

Hearing: The loss of hearing in older dogs and some cats is well-recognized.[17] Hearing loss associated with decreased sound wave conduction from the external ear to the cochlea (conduction deafness) can be helped with amplification. Dogs with fibrotic or ruptured tympanums fit into this category. Neurogenic deafness (sensorineural), i.e., specific loss of nerve function, is the most common cause of deafness in older dogs.[18] Amplification will not help this type of deafness. However, the use of a high-frequency dog whistle is a temporary solution until the higher frequency sound recognition is lost.

Vision: The normal aging changes in the lens called nucleus or lenticular sclerosis should be differentiated from opacities of the lens/capsule (cataracts). Lenticular sclerosis is never a cause for visual impairment. All cataracts should be staged to better assess the cataracts' impact on the patient's vision. If the problem is retinal, then cataract extraction would obviously not benefit the patient.

Central Nervous System Decline

Older animals undergo somewhat predictable personality changes with aging.[2] Most older pets need increasing amounts of attention and are exceedingly more jealous of new housemates and visitors. They are more irritable and less tolerant with once-endured actions of housemates, owners and visitors. Elderly pets are less mentally alert plus they sleep a larger percentage of time although the actual sleep patterns may be significantly altered. Most animals exhibit varying degrees of cognitive decline with age. Declines in the cognitive abilities of memory, learning, perception, and/or awareness are hallmarks of the progressive process.[16,19] For some patients, it is a significant issue resulting in quality of life issues and progressively unacceptable behaviors.

Declining Immunity

Immunosenescence refers to the gradual deterioration of

the immune system brought on by natural age advancement. It involves both the host's capacity to respond to infections and the development of long-term immune memory, especially by vaccination.[20] Decreases in both cellular and humoral immunity are closely associated with the aging process and should be considered a major contributory factor to the increased frequency of morbidity and mortality among older pets. The progressive decrease in the patient's immune status explains the increased prevalence of tumor growth and infection rates in geriatric patients. The inference is vaccine-induced immunity plus the routine use of immunostimulants.

Our goals should be to optimize the quality of life for the older pet, using preventive health care strategies combined with state-of-the-art diagnostics and therapeutics. Historically, veterinarians have only reacted to those diseases and age-related problems in elderly pets. We need to refocus our efforts on a proactive approach to older patients, and thus, not waiting until overt disease is present. The program should emphasize slowing the aging process, implementing steps for prevention and early detection of age-related diseases, plus vital client education programs.

Considerable research in the area of interrupting the aging process is ongoing in both humans and animals. Technologies such as gene splicing might someday allow each of us to live longer, more productive lives. Until then, decreasing known risk factors, along with implementing regular exercise programs, premium senior diets, and antioxidant supplements, are generally recognized as valuable anti-aging strategies.

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Q&A Discussion

Q: Dr. Joe Millward, University of Surrey: I was interested in what you said in relation to sensory decline and the eye. In the case of the aging human, there's a lot of interest in age-related macular degeneration. The growing research base suggests that it is a nutritionally sensitive disease with a growing evidence base for very long-chain omega-3 fatty acids and also some of the carotenoids. I wondered what the research base is like in the case of companion animals.

A: Dr. Fortney: Since dogs do not have an anatomical macula, they do not experience macular degeneration. However, the question whether nutritional deficiencies may be a cause for some of the visual impairments we see in dogs is a good one. Unfortunately, I do not know the answer to that question.

Q: Dr. Barb Kitchell, Michigan State University: The oncology literature is obviously gerontology literature, and one of the things that is addressed a lot in that aspect is some of the cellular changes that take place around being unable to balance redox, free radical scavenging, DNA repair and things like that. Do you know, is there any validity to trying to do something with antioxidants from a nutritional standpoint in trying to mitigate some of these age-related changes?

A: Dr. Fortney: Yes, I routinely prescribe antioxidants to all my senior patients, whether it's in a dietary form or as a supplement. I think there's enough scientific evidence that it may help slow the aging process. I'm all in on that one.

Q: Dr. Joe Wakshlag, Cornell University: I'd like to comment on Barb's question. Within the oncology literature, which I refer to all the time, is a study from Purdue looking at traditional cell carcinoma in Scottish Terriers. From that data, the incidence of that disease is lower when those dogs are put on some sort of vegetable matter as a treat or part of their diet, something that is missing in a lot of dog foods today. So, is that something we should be addressing as a dietary factor that needs to be put into foods to essentially mitigate those kinds of problems?

Dr. Barb Kitchell: And just to come back with that a little bit, you are referring to natural products, dietary sources of antioxidants versus supplements. One of the biggest problems we have in the oncology community is these patients who come in with like 27,000 supplements and who knows what anything is actually doing. So, it becomes a bit of a conundrum for us because some of our therapeutics are redox-dependent in their anti-cancer effect, but we have these patients who are on massive levels of various antioxidants, and what does that do? The literature is very unconvincing in terms of antioxidant effect in patients with cancer, or at least mixed in terms of antioxidant effect and outcomes from either radiation or chemotherapy.

A: Dr. Fortney: I think there are two pieces of business here: One is therapeutic use of antioxidants and the other strategy is preventive, trying to slow the routine aging process by using the antioxidants. I'm a firm believer that dietary antioxidants are the best way to go.

Dr. Joe Wakshlag: Getting back to Joe Millward's question with reference to the human diet, we talk about antioxidant consumption being deficient in one individual and very high in another. A lot of dog foods tend to be made with mixed tocopherols, which are natural antioxidants, as well. So I would say that a lot of dogs are getting this wonderful antioxidant dose at least with tocopherols. So, is that enough? I don't know, but it does point out a very different way of feeding in the human world and the canine world.