Chapter 35

Cognitive Dysfunction in Dogs

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"Dogs' lives are too short. Their only fault, really."
Agnes Sligh Turnbull

CLINICAL IMPORTANCE

Current estimates suggest that approximately 20 to 30 million dogs over the age of seven years live in the United States, representing 30 to 40% of the total canine population (AVMA, 2002). Behavioral changes, the development of new behavioral problems and the exacerbation of previous behavioral problems occur commonly with increasing age. At one animal behavior referral clinic, the most common complaints cited by pet owners included increased incidence of separation anxiety, house soiling, phobias, waking at night and excessive vocalization (Chapman and Voith, 1990). In addition, memory impairments, symbolic recognition and object permanence were associated with aging in dogs (Dehasse, 2005).

Canine cognitive dysfunction syndrome (CDS) is the name proposed to describe behavioral changes noted in client-owned aged dogs (Ruehl et al, 1995). Numerous owner-based observational studies have assessed the prevalence of CDS. For example, 180 dogs that had been determined to be healthy at their annual visit were reevaluated by client telephone followup; 28% of owners of 11- to 12-year-old dogs and 68% of owners of 15- to 16-year-old dogs reported at least one sign of CDS (Neilson et al, 2001). (See disorientation, alterations in interactions with people and other pets, alterations in sleep-wake cycles and house soiling [DISH] below.) In another study of 102 dogs eight years old and older, in which underlying medical problems had been ruled out, 41% had alterations in one category, whereas 32% had alterations in two or more categories of DISHA (See definition below) (Osella et al, 2007).

PATIENT ASSESSMENT

History, Screening Questionnaires and Other Clinical Information

Behavioral signs reported by pet owners are the primary criterion upon which to base a diagnosis of cognitive dysfunction (**Table 35-1**). However, the diagnosis can only be made after exclusion of all other medical problems that may cause similar clinical signs. For example, any change in personality or mood, inability to recognize or respond appropriately to stimuli or loss of previously learned behavior may indicate diseases of the forebrain or may arise from sensory system deficits. Diseases of virtually any other organ system can also affect behavior and these are discussed in more detail elsewhere (Landsberg and Araujo, 2005; Landsberg et al, 2003). Chronic or recurrent stress and anxiety can also affect health and behavior, in part by affecting the hypothalamic-pituitary axis and possibly by overstimulation of the noradrenergic system. Therefore, reporting any change in behavior is essential for the health and well-being of all pets, and, in particular, for senior pets, in which degenerative diseases, tumors, pain and discomfort are increasingly common.

In 2005, the American Animal Hospital Association senior care task force published guidelines that recommend yearly

Table 35-1. Behaviors evaluated in dogs to assess age-related cognitive decline.*

1. Confusion, awareness, spatial orientation
Gets lost in familiar locations
Goes to wrong side of doors (e.g., hinge side)
Gets stuck and cannot navigate around or over obstacles
Less responsive to stimuli
Decreased recognition of familiar people, pets or places
2. Relationships and social behavior
Decreased interest in petting or contact
Decreased greeting behavior
Alterations or problems with social hierarchy
In need of constant contact (e.g., over dependent or "clingy")
3. Activity: Increased, decreased or repetitive
Decreased daytime sleep/increased wandering or pacing
Decreased exploration (apathy)
Staring, fixation or snapping at objects
Licking owners or household objects
4. Agitation or anxiety
Inappropriate vocalization
Restless sleep
Increased irritability/aggression
Aimless pacing and wandering
Increased/new fears or phobias
Separation anxiety
5. Appetite
Increased interest (volume eaten or speed of eating)
Decreased interest
Anxiety–conflict behaviors at food bowl
6. Decreased responsiveness to stimuli
May seem to have a decline in vision, hearing or odor perception
7. Decreased self-care
8. Sleep-wake cycle
Restless sleep or awake at night
Increased daytime sleep
9. Learning and memory
a) House soiling: Indoor elimination at random sites or in view of owners
Decreased or no signaling
Goes outdoors, eliminates indoors upon return
Elimination in crate or sleeping area
Incontinence
b) Works, tasks, commands
Impaired working ability
Impaired responsiveness to known commands or tricks
Decreased ability to perform tasks
Inability or slow to learn new tasks (must retrain)
*Adapted with permission from Landsberg G, Hunthausen W, Ackerman L. The effects of aging on behavior in senior pets. Handbook of Behavior Problems of the Dog and Cat. Edinburgh, Scotland: Elsevier Health Sciences, 2003.

wellness screening for healthy middle-aged pets and twice yearly screening for senior pets (i.e., last 25% of predicted lifespan). At each visit, the pet should receive a physical examination and laboratory tests and the owner should be extensively questioned about changes in behavior and health (Epstein et al, 2005). Most of these changes would not be detected during a veterinary visit because they can be intermittent, subtle in onset and only noticeable in other environments. Therefore a senior care program should include use of a screening questionnaire (**Table 35-1**). (Landsberg and Araujo, 2005; Landsberg et al, 2003; Pfizer Animal Health) and/or allow sufficient time for interactive history taking. If problems are identified, early intervention may improve quality of life and longevity.

The reliability and usefulness of brain imaging for detection of CDS has not been systematically examined. However, in some cases, a magnetic resonance imaging (MRI) scan might be useful for differential diagnosis. Imaging might allow practitioners to rule out alternative explanations for changes in behavior, such as the presence of gliomas, tumors or damage due to stroke. Note that a normal MRI scan cannot be used to rule out CDS. However, with increased age, there is a tendency toward ventricular dilatation and neuronal loss. (See macroscopic changes below.) Although these changes might be expected to correlate with increasing cognitive dysfunction, this has not been validated. Traditionally, the signs of canine CDS, hypothesized to be caused by brain aging, were described by the acronym DISH. (See above.) Alterations in activity levels including increased restlessness and pacing have also been identified; therefore, an "A" for activity has more recently been added to the acronym (Landsberg and Araujo, 2005; Landsberg et al, 2003; Neilson et al, 2001; Osella et al, 2007). These signs, however, do not necessarily reflect all of those associated with CDS and brain aging.

In a review of 50 recent Veterinary Information Network (VIN) postings of behavioral signs in senior dogs (aged nine to 17), many of the reported problems were related to agitation and anxiety including fear, excessive vocalization, salivation, destructiveness, hypervigilance, over-attachment, separation anxiety, night-time waking and anxiety, restlessness, wandering, pacing, confusion, noise phobias, increased sensitivity to sound, compulsive licking and aggression (sometimes concurrent with and sometimes independent of other signs of DISH). Each case received the guidance of one or more of the VIN specialists in neurology, internal medicine or behavior. Seizures, hypertension, sensory decline, arthritis, pituitary-dependent hyperadrenocorticism and cerebral disease were the most commonly suggested rule outs. There was no identifiable medical cause in 24 of the 50 cases, and medical problems were deemed unlikely to have contributed to the behavioral signs in another nine cases. Of the remaining cases, arthritis, hearing loss, renal insufficiency, lymphadenopathy, mild anemia and pharmaceutical therapy such as phenylpropanolamine and prednisone were considered as possible contributing factors. This underscores the importance of ruling out medical problems that might cause clinical signs, and the fact that anxiety and agitation are commonly reported signs in senior pets.

A number of cognitive disorders have been described in the French literature including confusional syndrome, dysthymic disorder and involutive depression (which may be associated with compulsive and stereotypical behavior, hyper-attachment, vocalization and anxiety) (Landsberg and Araujo, 2005). In addition, laboratory studies indicate that there is a measurable decline in learning and memory associated with brain aging. Laboratory-based systematic studies of changes in behavior and cognition also provide evidence that behavioral changes in senior dogs observed clinically have a neurobiological basis. Thus the acronym DISHA may not sufficiently and accurately reflect all of the clinical signs associated with brain aging and cognitive dysfunction in older pets. Because these signs are generally noticed by pet owners and seldom in the veterinary clin-

ic, pet owners should be counseled to immediately report any changes in behavior or health in older pets. In turn, veterinarians should use these signs, along with results of physical and neurologic examinations and results of other diagnostic testing to diagnose or rule out possible systemic causes, and to determine if the signs may be associated with brain aging. The use of a cognitive assessment questionnaire may help facilitate the process (**Table 35-1**).

Although feline data are much more preliminary, **Box 35-1** describes clinical observations of CDS, age-related neuropathology and treatment of CDS in cats.

Relationship Between Age, Cognitive Dysfunction and Pathology: Laboratory Studies

Changes in Cognitive and Non-Cognitive Behaviors with Age

Although owner-based survey studies are informative for assessing global brain function, using laboratory-based neuropsychological tests represents a more systematic approach to detect subtle and early changes in learning and memory with age that might go unreported in the clinic. By contrast, owner assessment is generally unable to detect changes in learning or memory, because house soiling and the level and extent of commands that the pet has learned are the only values that can be assessed, except perhaps in performance, working or assistance dogs in which a higher degree of training and learning has been attained. A modified Wisconsin General Testing Apparatus (**Box 35-2**) is one laboratory-based method used to detect early changes and systematically characterize changes in cognition in aging beagles (Milgram et al, 1994). An array of tasks has been developed to measure specific cognitive abilities in dogs. These tests include assessment of associative learning in which a dog must learn that only one of two objects hides a food reward based on shape (Head et al, 1998), size (Head et al, 1998; Tapp et al, 2003) or spatial location (Christie et al, 2005; Milgram et al, 1999) of the object. There are also tasks that assess how long a dog can remember if it has seen a particular object (Callahan et al, 2000) or spatial location (Adams et al, 2000; Chan et al, 2002) and tests of executive function that assess how readily it can learn a particular rule or strategy for solving a task (Tapp et al, 2003a, 2004a).

Cross-sectional and longitudinal studies using these tests indicate that cognition declines with age in dogs, but that the decline is selective to certain cognitive abilities and tasks. Procedural learning, or the ability to remember particular skills or habits necessary for success in the Toronto General Testing Apparatus, remains relatively intact in old dogs (Milgram et al, 1994), whereas tests of executive function and working memory are highly sensitive to aging (Christie et al, 2005; Tapp et al, 2003, 2004). For example, young and old dogs are easily trained to associate one object in a pair of stimuli with a food reward when the object pair is presented repeatedly over several test trials (Adams et al, 2000; Christie et al, 2005; Milgram et al, 1994). At this stage, no age differences in learning are found, suggesting that simple visual processing remains intact in aged animals. If, however, the reward contingency is reversed such that the opposite stimulus becomes associated with food reward, some senior dogs are unable to change their response pattern (Christie et al, 2005; Head et al, 1998; Tapp et al, 2003, 2004). This indicates that age affects cognitive flexibility, or the ability to modify previously formed associations, which suggests changes in frontal lobe function in aged dogs (Tapp et al, 2004).

Table 35-2. Laboratory deficits and tentative clinical correlates in age-related cognitive dysfunction syndrome in dogs.

Laboratory deficit	Clinical signs
Impaired spatial learning	Disorientation in space, time
Impaired spatial memory	Disorientation in familiar surroundings
Impaired oddity and discrimination learning	Impaired symbolic recognition, object permanence
Executive dysfunction	Deterioration of social skills, increased house soiling
Disrupted sleep-wake cycle	Wandering at night
Altered locomotion in open field	Altered activity levels

Aged dogs also have impaired ability to acquire and remember an oddity discrimination task (Milgram et al, 2002). In this paradigm, the animal is presented with three objects; two are identical but one differs in size, shape and color. The dog must learn that the odd object hides a food reward and remember to choose the odd object when tested at a later occasion on other oddity discrimination levels. There are four levels to the oddity task and each successive level becomes more difficult by increasing the similarity of the odd object to the identical pair of objects. Old dogs learn all oddity levels more slowly than young dogs. Furthermore, this age effect is particularly pronounced as the task increases in difficulty (Milgram et al, 2002).

The precise link between clinical measures of CDS and systematic laboratory cognitive tests is unknown. Currently, we can only speculate as to which laboratory-based deficits might correspond to clinical signs reported to occur in dogs with CDS (**Table 35-2**). For example, the owner-observed disorientation in space and time might correspond most closely with neuropsychological tests of spatial learning and memory. More research is needed to determine if results from the laboratory translate directly to the clinic and if tests of cognitive function in laboratory-based tasks involve the same brain circuits that are compromised in CDS. This would be accomplished, in part, by conducting both neuropsychological tests and in-home behavioral questionnaires on the same group of dogs. Currently, this is not a practical option because home tests would need to be developed and standardized.

Laboratory studies provide evidence that aged dogs develop changes in overall activity and in cognition. Studies identify differences in young and aged beagles in exploration (as measured by response to novel toys) and social responsiveness to a passive human subject. Although aged dogs with minimal evidence of cognitive impairment may have decreased activity, cognitively impaired aged dogs show increased sporadic activity levels, but decreased social responsiveness and exploratory behavior (Siwak et al, 2001, 2003). This may correlate with the initial decline in activity and increased sleep reported clinically in

Box 35-1. Clinical Observation of Cognitive Dysfunction Syndrome in Cats.

The presenting complaints of 83 senior cats referred to veterinary behaviorists were house soiling (73%), intraspecies aggression (10%), aggression toward people (6%), excessive vocalization (6%), restlessness (6%) and excessive grooming (4%). However, there is a much wider range of subtler and more frequent behavioral changes seen by owners that may not be reported and are unlikely to require referral.

A second study was intended to evaluate the prevalence of clinical signs in a population of otherwise healthy cats that were presented for annual examination or other routine care. Owners of 154 cats aged 11 and older were asked, using a questionnaire (similar to the canine questionnaire in **Table 35-1**), about whether their cats showed any behavioral signs such as altered activity levels, increased anxiety, night waking, increased vocalization, house soiling, altered responsiveness to stimuli, alterations in interactions with people or other cats and evidence of confusion or disorientation. After removing cats with medical problems, 50% of those aged 15 years or older were diagnosed with cognitive dysfunction syndrome (CDS); altered activity levels, aimless activity and excessive vocalization were reported most commonly. Additionally, 28% of cats aged 11 to 15 years had signs of CDS; altered social interactions were reported most commonly.

In an attempt to further determine some of the more common behavioral problems for which owners seek veterinary advice, 100 recent Veterinary Information Network (VIN) postings about senior cat (aged 12 to 22 years) behavioral problems were reviewed. The most common complaints were vocalization, altered sleep-wake cycles, night-time anxiety, nighttime restlessness, inappropriate elimination including spraying, confusion, disorientation, wandering, pacing, anxiousness, restlessness, irritability, aggression, fear/hiding, increased attachment/"clingy" behavior and decreased interaction with owners. A few problems were reported in only single cats. These included departure anxiety, pica (cardboard) and scratching. Pain (e.g., arthritis, dental), decreased mobility, metabolic problems including hyperthyroidism, renal and hepatic disease, hypertension, concurrent drug therapy, vision or hearing loss and forebrain lesions (particularly meningiomas) were the primary rule outs suggested by VIN specialists. Although many of these cases had sufficient workups to rule out all possible medical causes including physical and neurologic examinations, urinalyses, blood tests (including thyroxine measurement), radiographs and blood pressure evaluation, few cats had magnetic resonance imaging. Furthermore, the effects of arthritis and hearing and vision loss were difficult to assess. In 11 cases, a recent change in the household including the death of another pet may also have contributed to anxiety. In comparison to the canine data (See text.), there were far more feline cases in which concurrent medical conditions could not be entirely ruled out. Thus, although signs of anxiety are common in aging cats, age-related brain pathology (CDS), environmental changes and medical problems might be factors. Conversely, the diagnosis of a medical problem does not exclude CDS because both could exist concurrently.

To date, few systematic laboratory studies have looked at changes in cognition across the lifespan of cats. As described above, however, owners of senior cats report age-related behavioral problems. It is also known that cats develop age-related neuropathology that theoretically underlies cognitive decline (described in detail below). For example, one study found that development of diffuse senile plaques in the brains of three aged cats was correlated with behavioral changes including wandering, confusion and inappropriate vocalization. In a more recent study, a range of cognitive deficits from mild to severe, including wandering, inappropriate vocalization, confusion/getting lost, decreased grooming, lethargy, loss of housetraining and decreased affection and recognition of owners, was reported in four out of five cats aged 16 years and older. Development of laboratory-based tests for cats will allow the correlation of age-related behavioral problems with neuropathological changes and may allow detection of cognitive decline in younger cats, as has been found in dogs.

AGE-RELATED NEUROPATHOLOGY IN CATS

Beta-amyloid (Aβ) has also been studied in the brains of cats although not as extensively as in dogs. The first study to look at Aβ pathology in cats consisted of immunohistochemical staining of the brain of three family cats aged 15, 16 and 20 years old. According to their owners, all cats exhibited abnormal behavior within the final years of life including wandering, confusion and night-time howling. The 20-year-old cat was specifically described as having behavior "suggestive of Alzheimer's Disease." Pathologic analyses revealed that all three cats displayed age-dependent increases in Aβ pathology very similar to that found in aged dogs, with diffuse deposits (sometimes spanning the entire cortical depth) and smaller, denser deposits in various cortical layers. Senile plaques were also assessed in seven aged cats of various breeds (12 to 20 years old) that had no abnormal behavioral reports when they were alive. In this study, only three aged cats, two 18 year olds and one 20 year old, had senile plaques that were immunoreactive for Aβ in the temporal and occipital cortex. In another study in which the brains of seven Siamese and seven domestic shorthair cats (aged 7.5 to 21 years old) were examined, Aβ deposition was detected by various antibodies in different brain structures of all 14

aging dogs, which then progresses to repetitive behaviors, restless pacing and compulsive disorders.

Risk Factors

Age is a risk factor for CDS. Behavioral disturbances are reported with increasing frequency in dogs around 11 years of age (Bain et al, 2001; Landsberg et al, 2003; Neilson et al, 2001). Initially, these changes might be subtle and seem innocuous to the client; however, in many cases they progress to include more clinical signs and/or signs of increasing severity that affect the pet's quality of life and the owner's ability to care for the pet. For example, in one study, 22% of senior dogs that had no impairments at an initial interview developed at least one sign of CDS at a followup interview 12 to 18 months later. In the same study, 48% of dogs that initially displayed one behavioral disturbance had impairments in two or more categories at followup (Bain et al, 2001).

To date, age is the only risk factor for CDS that has been systematically studied in the clinic and laboratory, although other risk factors are possible, such as breed (larger breeds might have an earlier age of onset), previous head trauma or occurrence of microvascular accidents. Consistent breed differences in susceptibility to CDS have not been reported; however, a potential genetic predisposition for development of CDS can be inferred

cats. One 12-year-old Siamese cat had a notable amount of Aβ plaques in the hippocampus, but diffuse Aβ plaque pathology was most likely to occur after 17 years of age. A study looking at very young and very old cats found that Aβ abnormalities were not observed in very young cats (<4 years old), but diffuse plaques were common in the brains of aged cats (16 to 21 years old). A more comprehensive study involving 19 cats (aged 16 weeks to 14 years old) found that 17 cats had clinical signs of neurologic dysfunction. Diffuse Aβ plaque deposition was observed beginning at 10 years of age and increased with age. Collectively, the Aβ neuropathological findings in cats show that, in comparison to dogs, which have Aβ deposition beginning at middle age, feline Aβ plaques appeared towards the end of the lifespan.

TREATMENT OF CDS IN CATS

Although no food is commercially available for cats with cognitive dysfunction, it is not unreasonable to believe that many of the same therapeutic options may be effective because cats have many of the same brain changes and behavioral signs associated with age as dogs and people. However, care must be taken when recommending off-label inclusion of some supplements such as α-lipoic acid because it is not metabolized as quickly in cats as in dogs. Therefore, although there is only anecdotal evidence of efficacy, some dietary supplements such as Senilife[a] are marketed for use in cats. There are no drugs licensed for treatment of cognitive dysfunction in cats, but selegiline, propentofylline and nicergoline have been used in cats with varying degrees of success.

As in dogs, treatment of clinical signs associated with brain aging such as vocalization, night waking or an increase in anxiety may also necessitate the use of anxiolytics drugs such as buspirone, benzodiazepines that have the least potential for hepatotoxicity such as oxazepam and antidepressants with no anticholinergic effects such as fluoxetine or pheromones such as Feliway.[b] It would be prudent to evaluate the effects of possible feline therapies either in the laboratory or clinic because aged cats may have compromised function and dose response data are limited.

ENDNOTES

a. Ceva Sante Animale, Libourne Cedex, France.
b. Veterinary Products Laboratories, Phoenix, AZ, USA.

The Bibliography for **Box 35-1** can be found at www.markmorris.org.

from reports of increased concordance rates of beta-amyloid plaque pathology (discussed in detail below) in littermates. In one study of aged dogs, the authors reported significant familial influence on plaque development by observing congruence in 15 of the 16 litters examined (Russell et al, 1992). Previous head trauma or occurrence of microvascular accidents may predispose animals to CDS by affecting the integrity of the blood-brain barrier (BBB), although no clinical data are available for definitive conclusions. In laboratory beagles, increases in BBB permeability with age in conjunction with the presence of vascular amyloid pathology suggest that disruptions to vascular integrity may be a risk factor for development of CDS (Su et al, 1998).

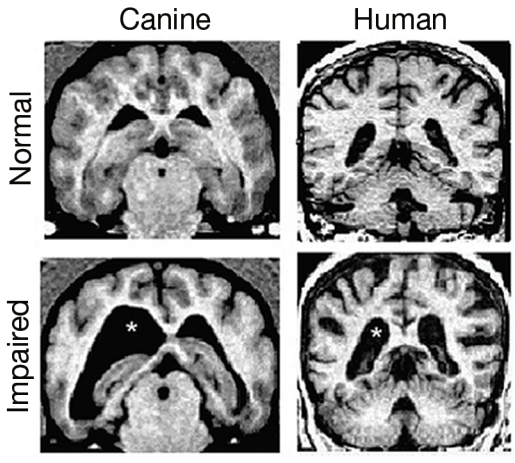

Figure 35-1. Magnetic resonance imaging of canine and human brain. Coronal sections of a cognitively normal beagle and person reveal structural similarities and a well-developed cortex. However, cognitive impairments are associated with enlarged ventricles (*) and general cortical atrophy of the gray and white matter, resulting in deep gyri and widened sulci. (Courtesy Dr. Min-Ying Su, University of California-Irvine.)

Etiopathogenesis

Cognitive changes in learning and memory often coincide with neuropathological changes in the brain. Despite the concomitant and statistically significant occurrence of various pathologic changes with deficits in cognition, to date, these studies remain largely correlative rather than directly causative. The following sections describe macroscopic and microscopic changes in the brains of dogs with cognitive dysfunction. See **Box 35-1** for information about age-related development of neuropathology in cats.

Macroscopic Changes in the Aging Brain

Changes in overall brain structure and volume can be seen using noninvasive techniques such as MRI. MRI studies in dogs reveal decreased brain volume, increased ventricular volume, increased perivascular space, lesions and cortical atrophy of the gray and white matter that often correlate with increasing age and cognitive decline (Su et al, 1998, 2005) (**Figure 35-1**). In 18 beagles (four to 15 years old), ventricular size increased slowly until 10 years of age and progressed very rapidly thereafter. In a longitudinal study using 47 beagles (eight to 11 years old at the first MRI), serial MRIs over four years revealed yearly increases in ventricular volume. Furthermore, different regions of the canine brain may have differing vulnerabilities to the aging process. An MRI study of 66 beagles (three months to 15 years) revealed decreases in total brain volume in dogs 12 years and older, whereas frontal lobe atrophy began much earlier, at eight years of age and correlated with impaired cognitive functions thought to be mediated by the frontal cortex (Tapp et al, 2004).

Lesions in aged beagles can be detected visually by MRI or by postmortem analysis of the brain. The cause and effect of these apparently spontaneous lesions is unclear; however, they have the morphologic appearance of lacunar infarcts or cysts

Box 35-2. The Toronto General Testing Apparatus.

The Toronto General Testing Apparatus (TGTA) is a canine-modified version of the Wisconsin General Testing Apparatus used for nonhuman primates. During testing, this wooden apparatus (**Figure 1**) houses the dog in a space (A) that contains no distinguishing features that a dog can use as cues for solving tasks. The experimenter is separated from the dog by a screen with a one-way mirror and a hinged door (B) that is opened for presentation of a sliding stimulus tray (C). The front of the TGTA is equipped with height- and width-adjustable bars (D) through which the dog accesses the stimulus tray, which contains one medial and two lateral food wells. The dog uses its nose to displace a stimulus and retrieves a highly-palatable cube of wet dog food when it makes a correct response. No food reward is given for an incorrect response. All stimuli used in tasks are baited with the same food in such a way that the dog can smell it but not see or eat it. This has the effect of masking any odor from the reward food cube so that it cannot be used as a cue to locate the correct stimulus.

Dogs first undergo a pretraining period during which they are exposed to the testing room and TGTA. They are encouraged to climb the stairs, enter the apparatus and eat food from the wells of the stimulus tray. After the pretraining phase is complete, a battery of cognitive tasks ranging from simple two-choice discrimination tasks to complex tests of executive function can be employed to provide objective and quantifiable measures of learning, memory and cognition. In addition, the TGTA can be used to assess attention, sensory and motor function, and recently, a paradigm was developed for evaluating dog food palatability. Cross-sectional studies using dogs of various ages are used to determine how learning is affected by age, and longitudinal studies are used to assess task retention across the lifespan.

The Bibliography for **Box 35-2** can be found at www.markmorris.org.

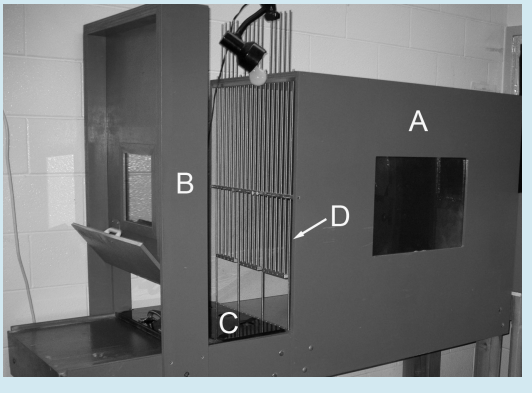

Figure 1. The Toronto General Testing Apparatus used to conduct cognitive testing in dogs. Test apparatus (A) where the dog is housed during testing, screen (B) to separate dog from experimenter with one-way mirror, sliding stimulus tray (C) with three food wells, height- and width-adjustable gates (D) allowing access to stimulus tray. (Courtesy Dr. Lori-Ann Christie, University of California-Irvine.)

and may be related to cerebrovascular changes in the aging brain. MRI lesions in beagles appear as hypointense cavities distributed throughout the brain, but are found most commonly in the frontal cortex and caudate nucleus (Su et al, 2005). In a group of 47 beagles imaged longitudinally over four years, lesions were observed starting at 11 years of age and became increasingly common by the time dogs were 14 years old (Su et al, 2005). Currently, the exact implications of these lesions are unknown and they may be clinically "silent."

Microscopic Changes in the Aging Brain

Microscopic signs of brain pathology can be observed in aged beagles with cognitive dysfunction. One type of pathology of significant interest is the accumulation of a protein fragment called beta-amyloid (Aβ). Aβ contains 39 to 43 amino acids and is the primary constituent of amyloid plaques in the brains of people with Alzheimer's disease (**Box 35-3**). Aβ is toxic to neurons in the brain and accumulates in diffuse proteinaceous plaques that are thought to play a causative role in the development of Alzheimer's disease in people (Selkoe, 2000).

Aged dogs naturally accumulate Aβ protein, with the exact same amino acid sequence, and with a similar extracellular pattern of deposition as occurs in people (Head et al, 2000; Johnstone et al, 1991). The brains of 40 beagles (two to 18 years old) were assayed for Aβ deposition; it was found that cortical Aβ is deposited in a specific spatial and temporal pattern. The earliest and most consistent area of Aβ, deposition was in the frontal cortex beginning at eight years of age, spreading caudally into the parietal and temporal/entorhinal regions by age 10 to 12 years, with the occipital cortex being the last to develop deposition at 13 years of age (Head et al, 2000). Other studies involving larger cohorts (more than 100 dogs) confirm that Aβ deposition is an accumulative and age-dependent process (Russell et al, 1996; Czasch et al, 2006). The Czasch et al 2006 study involving 130 dogs (one month to 18 years) revealed only one dog with pathology in the one month to seven years of age category, whereas 47% had Aβ deposition between the ages of eight to 10 years, 79% between 11 to 13 years and 91% between 14 to 18 years. Other studies involving dogs of different breeds (i.e., German shepherd dog, sheepdog, schnauzer, Doberman pinscher, poodle, Pekingese, fox terrier, beagle, caniche, boxer, Labrador retriever, collie, cocker spaniel, Irish setter, husky, mixed breed, etc.) also confirmed that Aβ deposition increases with age and severity of cognitive deficits (Anderson et al, 2000; Borras et al, 1999; Colle et al, 2000; Cummings et al, 1996; Hou et al, 1997; Pugliese et al, 2006, 2006a).

Aβ deposition has been studied more thoroughly in beagles than in other dogs. In this breed there are significant correlations with increased age and cognitive dysfunction (Cummings et al, 1996; Head et al, 1998; Tapp et al, 2004) and with decreased brain volume as determined by MRI (Tapp et al, 2004). Investigators selected 20 dogs (11 beagles) in one study and all dogs received a battery of six cognitive tasks (i.e., reward and object approach learning, discrimination and reversal learning, object recognition and spatial learning and memory). In this study, increased Aβ deposition was strongly associated with

Box 35-3. Similarities Between Neurologic Diseases in People and Those Found in Dogs.

The original rationale for conducting laboratory-based studies on canine cognition was to develop a model of human age-related cognitive dysfunction. The population of aged dogs tested to date display many similar characteristics to those observed in the aged human population. Like people, dogs show age-related individual variability in their learning, memory and cognitive abilities, and these impairments vary as a function of task. Some old dogs perform neuropsychological tests quite well for their age (successful agers), others are mildly impaired (similar to age-associated memory impairments in people) and still others are severely impaired (similar to dementia in people). Furthermore, neuropsychological tests developed for use in dogs have been adapted to test people. Preliminary evidence suggests that these adapted canine tasks are successful in discriminating healthy and cognitively impaired subpopulations of people.

Aged dogs develop similar neuropathological features to those in both successfully aging people and patients with Alzheimer's disease. As in people, beta-amyloid (Aβ) protein is deposited in the aging dog brain, and shows a selective distribution that changes as a function of age. Immunostaining of the frontal cortex with an anti-Aβ marker reveals morphologic similarities between Aβ plaques in the brains of normal and cognitively impaired people and beagles, making it very difficult to distinguish one species from another based on plaque deposition (**Figure 1**). Furthermore, the extent to which they possess these biologic markers is correlated with their cognitive abilities across the lifespan. For instance, results from a recent study show that decreased brain volume and increased Aβ load accumulation in the frontal cortex of aged dogs are correlated with deficits in complex discrimination and reversal learning.

Taken together, these findings suggest that the canine model can be used effectively for studying the etiology of age-related cognitive decline and dementia and their prevention and treatment in people. There are many research endeavors currently underway to determine if similar positive effects on cognition with antioxidant dietary intervention will be evident in people. This research represents a unique and exciting approach in translating what we know in dogs to aged and diseased human populations.

The Bibliography for **Box 35-3** can be found at www.markmorris.org.

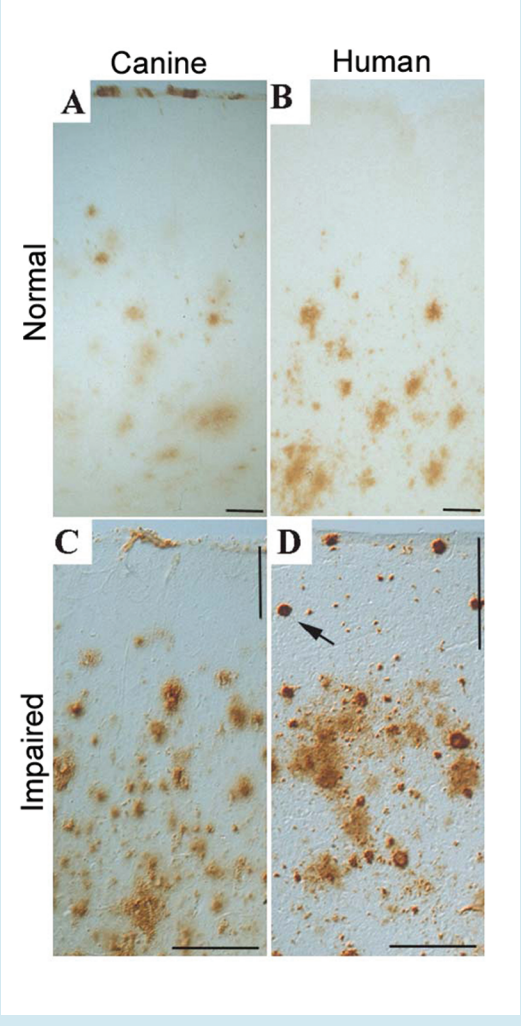

Figure 1. Comparable beta-amyloid (Aβ) immunostaining in the canine and human brain. The frontal cortex of a cognitively normal 13-year-old beagle (A) and 90-year-old female (B) illustrates a similar pattern of senile Aβ plaque deposition in the deeper cortical layers. Frontal cortex sections of a severely impaired 12-year-old beagle (C) and 86-year-old individual (D) with Alzheimer's disease show extensive Aβ pathology throughout all layers of cortex, whereas the molecular layer is largely spared (vertical line = molecular layer, arrow = compact plaque, all bars = 200 mm). (Reproduced with permission from Head E, Milgram NW, Cotman CW. Neurobiological models of aging in the dog and other vertebrate species. In: Hof P, Mobbs C, eds. Functional Neurobiology of Aging. New York, NY: Academic Press, 2001; 457-468.)

increased error scores across all tasks (Cummings et al, 1996) (**Figure 35-2**).

Functional Changes in the Aging Brain

In addition to macroscopic and microscopic morphologic changes in the aging canine brain, there is also evidence of functional change.

CHANGES IN THE BLOOD-BRAIN BARRIER WITH AGE

The BBB is a collective term for the complex vascular system of endothelial cells, astrocytes, pericytes and basement membranes surrounding the brain. The BBB allows for selective transport of nutrients from the blood to neuronal cells (Khan, 2005). An MRI study involving 18 beagles (four to 15 years old) showed a non-significant increase in BBB permeability with age; surprisingly, one six-year-old beagle, in which no pathology was expected, had severe BBB leakage and dysfunction, enlarged ventricles, Aβ deposition and cognitive dysfunction (Su et al, 1998). Another study reported a direct link between vascular Aβ deposition and vessel wall integrity; leptomeninges obtained from old dogs affected by cerebral amy-

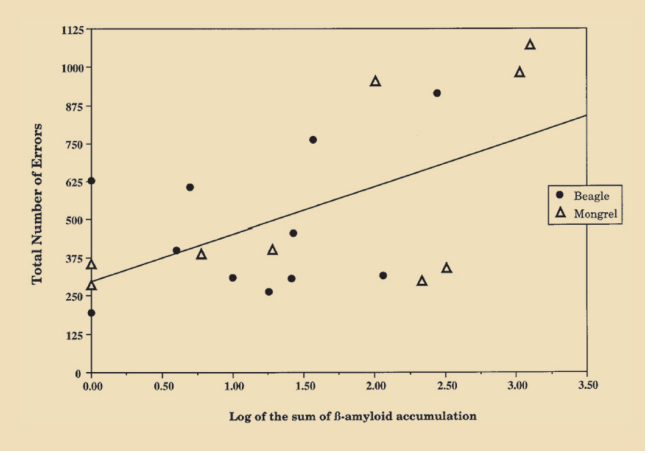

Figure 35-2. Correlations between cognitive task errors and beta-amyloid (Aβ) accumulation in beagles and mixed-breed dogs. The y-axis represents the summed error scores for a series of cognitive tasks and the x-axis represents the overall log scores of the Aβ load measurements from the frontal cortex, entorhinal cortex and cerebellum for each individual animal. Increased cognitive error scores were significantly correlated with increased Aβ measurements ($r = 0.66$, $p \leq 0.01$). (Reproduced with permission from: Cummings BJ, Head E, Afagh AJ, et al. Beta-amyloid accumulation correlates with cognitive dysfunction in the aged canine. Neurobiology of Learning and Memory 1996; 66: 11-23.)

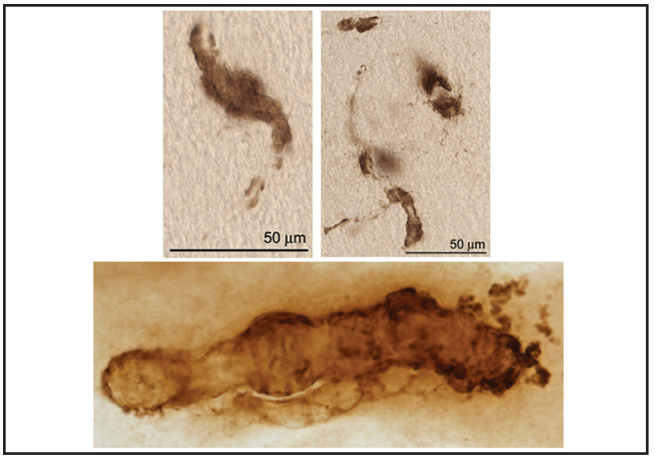

Figure 35-3. Amyloid angiopathy in the canine brain. All three panels illustrate immunostaining with beta-amyloid (Aβ) antibodies in the aged (~10 years old) canine cortex with vessels that are severely affected by Aβ deposition. Angiopathy can impair vascular function and damage the blood-brain barrier, leading to increased permeability of substances in and out of brain cells. (Courtesy Viorela Pop, University of California-Irvine.)

loid angiopathy showed segmental loss of vessel integrity at sites of Aβ deposition, suggesting that the presence of Aβ in old dogs disrupts the BBB (Prior et al, 1996). A study investigating the white matter of 31 dogs of various breeds (six months to 18 years old) found that age-related morphologic changes in the capillaries were associated with BBB permeability dysfunction. Specifically, aging dogs had degeneration of axons, perivascular infiltration of macrophages and iron and sometimes small foci of hemorrhages and infarction (Morita et al, 2005).

Recently, BBB permeability studies involving aged beagles treated with a food containing enhanced levels of antioxidants and/or behavioral enrichment found that, overall, there was a higher permeability index in the occipital lobe compared to the frontal and parietal regions (Su et al, 2006). In this same analysis, the occipital cortex had the highest amount of vascular Aβ pathology (**Figure 35-3**), which may have contributed to the increased BBB index in this region. Furthermore, yearly increases and worsening of BBB permeability were slowed in groups given antioxidant and/or enrichment treatment. Another study involving 25 dogs of various breeds (three to 19 years of age) found that scores on cognitive status questionnaires (Age-Related Cognitive and Affective Disorders) correlated with increased vascular Aβ deposition (Colle et al, 2000). More studies are underway to better understand BBB changes with increased age; interventions may prevent or delay BBB dysfunction and reduce the secretion of serum containing harmful substances that may further induce tissue damage and oxidative stress.

INCREASED OXIDATIVE DAMAGE WITH AGE

Oxidative damage is one possible mechanism that contributes to neuronal dysfunction and the progression of neuropathology with age. Normal metabolic processes in the brain lead to the production of oxidants, or reactive oxygen species (ROS). The free radical theory of aging (Harman, 1956) was the first to propose that excessive production of ROS leads to cell damage and that this damage accumulates over time and inevitably leads to age-dependent pathology in multiple tissues. ROS are the byproducts of mitochondrial aerobic respiration (Beckman and Ames, 1998), and include any atoms or molecules that contain one or more unpaired electrons. ROS are unstable because their unpaired electrons thermodynamically seek to pair with other electrons. This increases unregulated/nonspecific reactions that have enhanced potential for interaction, damage and dysfunction inside cells. Overproduction of ROS results in oxidative damage to proteins, lipids and nucleotides, which, in the brain, lead to neuronal dysfunction and untimely neuronal death. Therefore, the aging process might be mitigated by appropriate reduction of excessive ROS (Chapter 7).

Normal aerobic metabolism in mitochondria generates the superoxide ion, the ROS molecule of central interest. An appropriate balance between superoxide production and detoxification systems is essential to cellular health and intracellular metabolic signaling. Under normal circumstances, cells have a variety of mechanisms to detoxify superoxide (Head and Zicker, 2004). As mitochondria age or become dysfunctional from disease, defense mechanisms are compromised and/or overwhelmed and superoxide is produced in excess leading to uncontrolled reactions in cells (Ames et al, 1993; Cottrell and Turnbull, 2000).

In dogs, at least one defense system declines with age. Superoxide dismutase is present normally in the brain and acts to convert reactive superoxide ions to hydrogen peroxide, thereby decreasing oxidative damage to surrounding tissues. In fact,

one approved treatment for cognitive dysfunction, selegiline, has been shown to increase levels of superoxide dismutase in the brain (Carillo et al, 1994). This compensatory mechanism appears to be compromised in older dogs (Kiatipattanasakul et al, 1997). It has also been shown that oxidative damage to proteins (Head et al, 2002) and lipids (Rofina et al, 2004) accumulates in older dogs. These findings, in combination with age-related cognitive dysfunction and pathologic changes, suggest that decreasing oxidative damage in the brain might improve cognitive function in older dogs. Thus, dietary interventions that decrease specific types of oxidative damage may slow the progression of age-related cognitive decline in dogs.

Key Nutritional Factors

A longitudinal laboratory-based study and a randomized, controlled clinical field trial of the effects of a food enriched in a broad spectrum of antioxidants were conducted as described below. Subjects were assigned to receive either an enriched food (test food) or an extruded senior food (control food). The enriched food was supplemented with vitamins C and E, selenium, L-carnitine, α-lipoic acid, omega-3 fatty acids and a mixture of fruits and vegetables. Key nutritional factors for cognitive dysfunction are listed in **Table 35-3** and discussed in more detail below.

Table 35-3. Key nutritional factors for foods for dogs with brain aging and associated behavioral changes (cognitive dysfunction).*

Factors	Dietary recommendation
Vitamin E	Increase dietary antioxidants Provide foods with ≥750 mg/kg
Vitamin C	Increase dietary antioxidants Provide foods with ≥150 mg/kg
Selenium	Increase dietary antioxidants Provide foods with 0.5 to 1.3 mg/kg
L-carnitine	Increase mitochondrial cofactors Provide foods with 250 to 750 IU/kg
α-lipoic acid	Increase mitochondrial cofactors Provide foods with ≥100 mg/kg
Omega-3 fatty acids (docosahexaenoic and eicosapentaenoic acids)	Total omegas-3 >1%
Fruits and vegetables	1% of each of five vegetable and fruit ingredients

*Dry matter basis.

Antioxidants and Mitochondrial Cofactors

Antioxidants are substances that scavenge ROS and decrease the overall number of oxidants in a system (Ames et al, 1993; De Ruvo et al, 2000). Many antioxidant compounds such as vitamin E, vitamin C and trace minerals (e.g., selenium) are derived from food sources. Vitamin C is a water-soluble vitamin that helps replenish vitamin E. Mitochondrial cofactors (α-lipoic acid and L-carnitine) act to enhance the function of aged mitochondria so that fewer ROS are produced during aerobic respiration (i.e., they work to increase mitochondrial efficiency). L-carnitine is involved in lipid metabolism within mitochondria; α-lipoic acid participates in redox reactions and increases intracellular concentrations of glutathione, a primary water-soluble antioxidant within cells. Fruits and vegetables contain flavonoids and carotenoids, which have antioxidant activities as well.

One hypothesis is that adding increased amounts of these components to a food would reduce the amount of oxidative damage in two ways, by: 1) decreasing the production of ROS and 2) increasing the capacity to clear ROS, and that this would slow the progression of age-related pathologic changes and cognitive decline by reducing overall oxidative damage.

A longitudinal laboratory-based study and a blinded veterinary clinical field trial were conducted to assess the effectiveness of a food supplemented with antioxidants and mitochondrial cofactors in ameliorating cognitive decline in older dogs (Dodd et al, 2003). Results were used as grade 1 evidence-based nutritional research for the development of a commercial, antioxidant-enriched food.[a]

Investigators conducting the clinical field trial recruited dogs over seven years of age that had clinical signs in two or more DISH categories. The dogs were randomly assigned to two groups: one that was fed a commercial control food (n = 64) and one that was fed an antioxidant fortified test dog food[a] (n = 61). Owners rated their pet's behaviors before and on Days 30 and 60 of the dietary intervention. After 30 days of dietary intervention, owners reported significant improvements in the following categories: disorientation, interactive changes, sleep patterns and house soiling. By Day 60, owners reported that dogs receiving the test food improved in all four DISH categories (plus activity) whereas those fed the control food improved in only two categories. Dogs receiving the fortified food had improvements in awareness of their surroundings, family and animal recognition and interaction, enthusiasm in greeting and agility, and were reported to circle and house soil less frequently. Overall, the test food was better than the control food; dogs receiving it improved in 13 of 15 behaviors (87%) compared to four of 15 behaviors (27%) for dogs in the control group (Dodd et al, 2003; Zicker, 2005).

The laboratory-based study included 48 aged beagles (10 to 13 years old) and 17 young dogs (three to five years). Each age group was divided into an enriched food group (antioxidant) and a control food group; both groups were balanced for age and initial cognitive performance. The enriched food consisted of a variety of antioxidants, mitochondrial cofactors and dried fruits and vegetables. The control food was an identical base food adequate for senior dogs; however, it was not fortified with additional antioxidants and mitochondrial cofactors. Dogs were tested at several time points over two years after initiation of dietary intervention. Old dogs receiving the antioxidant food had improved learning and memory as measured by several cognitive tasks. The oddity discrimination task was administered, as described above, six months after the dietary intervention began (Milgram et al, 2002). Both age and food effects were observed (**Figure 35-4**); old dogs made more errors at learning all levels of the task compared to young dogs. However, old dogs fed the antioxidant food made significantly

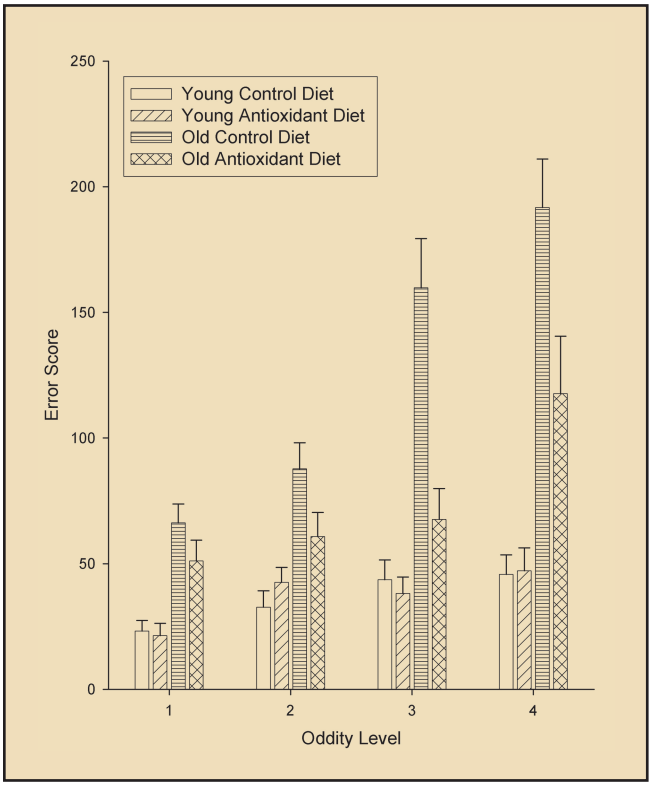

Figure 35-4. Effect of age, food and task difficulty on acquisition of an oddity discrimination learning task. Overall, the number of errors made to achieve the criterion increased with increasing oddity level; old dogs made more errors compared to young dogs on all levels. A food with enhanced levels of antioxidants and mitochondrial cofactors significantly reduced the number of errors made by old dogs to acquire the task. (Courtesy Dr. Elizabeth Head, University of California-Irvine.)

fewer errors than old dogs fed the control food. This effect was particularly pronounced at the most difficult oddity levels. Furthermore, the beneficial effect of the antioxidant food on oddity discrimination learning was not observed in young dogs, presumably because they did not have significant oxidative damage that could be reduced by dietary intervention like the older dogs (Head and Zicker, 2004; Milgram et al, 2002).

Positive antioxidant food effects were also observed selectively in old dog's reversal learning performance (Milgram et al, 2004, 2005). Dogs were first taught to respond to one of two stimuli to receive a food reward, as described above. There was no significant effect of diet at this stage of learning, which was anticipated given that simple discrimination learning, in general, remains intact in old animals (Milgram et al, 2005). However, when the reward contingencies for the task were reversed so that dogs had to suppress their tendency to respond to the previously rewarded stimulus and learn to choose the opposite stimulus, old dogs receiving the antioxidant food had improved learning compared to old dogs fed the control food. This effect of the antioxidant food on reversal learning was found when stimuli differed in size after one year of treatment and when they differed in intensity (e.g., black/white discrimination) after two years of treatment, indicating that the improvement in cognitive function was maintained over time (Milgram et al, 2005). Similar beneficial effects of the antioxidant food in old dogs have been observed with other cognitive tests, including a landmark spatial discrimination task as early as two months after the start of the trial (Ikeda-Douglas et al, 2004; Milgram et al, 2002), a complex size concept task (Siwak et al, 2005) and in contrast sensitivity discrimination (de Rivera et al, 2005).

Overall, the results demonstrate that the rate of cognitive decline observed in old dogs can be slowed by dietary intervention, and that the positive effects on cognition occur relatively rapidly. The findings also suggest that feeding a food containing a mixture of specific antioxidants and mitochondrial cofactors may act synergistically to reduce oxidative damage and increase mitochondrial efficiency, and that oxidative damage and mitochondrial function are fundamental mechanisms contributing to age-associated cognitive dysfunction in older dogs. More studies are currently underway to determine the specific combinations of ingredients that are most effective at ameliorating cognitive dysfunction in older dogs.

In the same laboratory-based intervention study in beagles described above, analyses of Aβ plaque deposition revealed that only dogs given the antioxidant food had less Aβ in the parietal and entorhinal cortex, but not in the prefrontal cortex (Pop et al, 2003). The food may prevent production of Aβ from its larger parent protein, Aβ precursor protein (APP), by increasing the activity of the alpha-secretase enzyme responsible for non-amyloidogenic APP cleavage (Pop et al, 2005). The results of the antioxidant study suggest that food can slow or prevent Aβ, deposition in regions actively accumulating Aβ (e.g., parietal and entorhinal), but cannot reverse existing deposits (e.g., those in the prefrontal cortex).

Appropriate levels of antioxidants and mitochondrial cofactors should be: vitamin E = ≥750 mg/kg; vitamin C = ≥150 mg/kg; selenium = 0.5 to 1.3 mg/kg; L-carnitine = 250 to 750 IU/kg; α-lipoic acid = ≥100 mg/kg; total omega-3 fatty acids = 1% added for docosahexaenoic and eicosapentaenoic acids; fruits and vegetables = 5% added for flavonoids and polyphenols, all on a dry matter basis. No minimum or maximum effective levels for fruits and vegetables have been established. The test food contained 1% of each of five vegetable and fruit ingredients as a substitute for corn.

A careful and detailed analysis of the concentrations of carotenoids, flavonoids and oxygen radical absorbance capacity of individual ingredients was necessary to develop the test food (Zicker, 2005). Studies of commodities with naturally occurring and synthetic antioxidants were conducted to ensure stability through processing, absorption from the gastrointestinal tract, safety and potential antioxidant biologic benefit. The results of these analyses highlighted that the mere presence of a fruit or vegetable on a label was not always indicative of high antioxidant content, an observation that practitioners and pet owners should take into account when choosing food for their senior pets.

Besides their apparent value in the dietary management of

Table 35-4. Recommended levels of key nutritional factors compared to the nutrient profile of a dry commercial food for canine cognitive dysfunction patients.*

	Energy density (kcal/cup)**	Energy density (kcal ME/g)	Vitamin E (mg/kg)	Vitamin C (mg/kg)	Selenium (mg/kg)	L-carnitine (mg/kg)	α-lipoic acid (mg/kg)	Total omega-3 fatty acids (%)	Fruits/ vegetables
Recommended levels	–	–	≥750	≥150	0.5-1.3	250-750	≥100	>1%	Added
Hill's Prescription Diet b/d Canine	358	4.0	1,075	109	na	299	na	1.02	Added

Key: na = not available from manufacturer
*Values obtained from manufacturer's published information. Nutrients expressed on a dry matter basis, unless otherwise stated.
**Energy density as fed is useful for determining the amount to feed; cup = 8-oz. measuring cup; to convert to kJ, multiply by 4.184.

CDS, antioxidants have been shown to play a role in the prevention of certain cancers through various mechanisms (Chapter 30). As in people, increasing age is a general risk factor for cancer in dogs.

Other Nutritional Factors

Older dogs are at increased risk for other diseases, including chronic periodontitis and osteoarthritis. Therefore, the clinician must choose the food based on which medical condition is of greatest priority for the pet. For example, cardiovascular and chronic renal failure may become more of a priority than cognitive dysfunction, necessitating reduced levels of sodium and phosphorus in the food. When the pet's health necessitates the use of a food other than one designed to promote optimal cognitive function, then specific supplements may need to be considered. However, the clinician should evaluate the evidence supporting the efficacy of any supplements that might be added to the feeding plan regimen and ensure there is no contraindication to their use.

FEEDING PLAN

The dietary goals are to provide a food that meets the patient's nutrient requirements and blunts the vulnerability of nervous tissue to ROS as the brain ages. Free radical damage can be manifested by behavioral changes or CDS. The food selected should contain levels of nutrients that protect against free radical damage and improve learning ability and alertness of older pets. Antioxidants and mitochondrial cofactors have demonstrated efficacy when fed in amounts as described in the Key Nutritional Factors section and shown in **Table 35-3**. Behavioral enrichment and medical therapy as described below may augment treatment.

Assess and Select the Food

Levels of key nutritional factors in foods currently fed to patients with cognitive dysfunction should be evaluated and compared with recommended levels. Information from this aspect of assessment is essential for making any changes to foods currently provided. Changing to a more appropriate food is indicated if key nutritional factors in the current food do not match recommended levels. **Table 35-4** provides the key nutritional factors recommended for foods for dogs with CDS and compares them to the key nutritional factor content of a commercial food developed specifically for dogs with CDS.[a]

Another criterion for selecting a food that may become increasingly important in the future is evidence-based clinical nutrition. Practitioners should know how to determine risks and benefits of nutritional regimens and counsel pet owners accordingly. Currently, veterinary medical education and continuing education are not always based on rigorous assessment of evidence for or against particular management options. Still, studies have been published to establish the nutritional benefits of certain pet foods. Chapter 2 describes evidence-based clinical nutrition in detail and applies its concepts to various veterinary therapeutic foods. Evidence Grade 1 (the highest level) exists for at least one food used for dogs with CDS.[a]

Assess and Determine the Feeding Method

A thorough assessment should include verification of the feeding method currently being used. Items to consider include feeding frequency, amount fed, how the food is offered, access to other food and who feeds the animal. All of this information should have been gathered when the history of the animal was obtained. If the animal has a normal body condition score (2.5/5 to 3.5/5), the amount of food previously fed (energy basis) was probably appropriate.

Adjunct Therapy

Behavioral Enrichment

Environmental enrichment (EE) also appears to play an important role in preserving cognitive abilities in old age. In dogs, there is laboratory-based evidence suggesting that an enriched environment acts synergistically with an antioxidant food to slow cognitive decline in older animals (Milgram et al, 2004, 2005). In the same study in which the fortified food was administered (described above), dogs in each of the food groups were further divided to include one group that received EE and one that did not. The EE program consisted of increased activity (i.e., exercise twice weekly), enriched kennel environments (i.e., toys and housing with kennelmates) and regular cognitive testing (i.e., neuropsychological testing five or six times weekly). In combination with the antioxidant food, positive effects of EE were observed after one year in the old dogs; size discrimination and reversal learning were improved. After two

years of EE, the enrichment alone was sufficient to detect improved performance on the intensity discrimination and reversal tasks. On both of these tasks, the investigators found that combined antioxidant dietary and EE intervention were more effective than either treatment alone. The authors concluded that a prolonged period of EE has substantial effects on cognitive performance in older beagles, and like the antioxidant food, appears to slow development of age-related cognitive decline in old dogs (Milgram et al, 2004, 2005).

Supplements

A number of complementary therapies are marketed as treatments for cognitive dysfunction. These products may contain mixtures of herbal extracts, vitamins, phospholipids, fatty acids, antioxidants and mitochondrial cofactors believed to act in a synergistic or potentiating manner to slow the progression of or improve clinical signs associated with brain aging. Although there is little evidence to support the efficacy of most of these products, three clinical trials have recently reported improvements in clinical signs of CDS in pets given dietary supplements containing phosphatidylserine (Osella et al, 2007; Cena et al, 2005; Heath et al, 2007). Phosphatidylserine, *Gingko biloba*, pyridoxine and vitamin E are distributed in Italy as a neuroprotective dietary supplement for senior dogs and cats.[b] In a preliminary laboratory evaluation, dogs were tested after administration of a placebo or the product for 60 days, in a crossover design using spatial memory assessments (Araujo et al, 2006). Performance accuracy was significantly improved in the treated group compared to the baseline group. In addition, dogs receiving the supplement in the first portion of the study maintained their improved performance (Araujo et al, 2006). This product was recently reformulated and now contains resveratrol.

Other commercially available supplements contain docosahexaenoic acid, eicosapentaenoic acid and acetylcysteine, which is a primary precursor to glutathione and coenzyme Q10. Fatty acids and glutathione may be beneficial in slowing brain aging in people (Horrocks and Yeo, 1999; Pocernich et al, 2000). Preliminary work also showed an improvement in memory and health status in dogs receiving a docosahexaenoic acid supplement (Araujo et al, 2005). S-adenosyl-methionine (SAMe) may be useful in elderly pets because it has been shown to be helpful for treating cognitive dysfunction in people. Furthermore, in a preliminary open label clinical trial, SAMe improved activity levels, sleep-wake cycles, playfulness and fecal elimination disorders in elderly depressed or confused pets[c] (Arnold, 2005).

Drug Therapy

Selegiline is licensed for treatment of cognitive dysfunction in dogs in North America.[d] Selegiline is a selective and irreversible inhibitor of MOA-B in dogs (Milgram et al, 1993). It increases 2-phenylethylamine in the canine brain. This drug is a neuromodulator; therefore, the primary mode of action may be to enhance dopamine and catecholamine function in the cortex and hippocampus to improve cognitive function (Milgram et al, 1993; Knoll, 1998). Selegiline may also contribute to a decrease in ROS in the brain by decreasing production of free radicals, scavenging oxygen free radicals and enhancing the scavenging action of enzymes such as catalase and superoxide dismutase (Carillo et al, 1994; Heinonen and Lammintausta, 1991). Selegiline is given at a dose of 0.5 to 1 mg/kg per os each morning. Although selegiline can be used concurrently with most veterinary therapeutic foods and supplements, it should not be combined with narcotics, antidepressants or monoamine oxidase inhibitors. Therefore, it should probably not be used with supplements containing tryptophan, St. John's wort or *Ginkgo biloba*.

Propentofylline and nicergoline, which may enhance cerebrovascular transmission, are licensed in some European countries and Australia for signs of brain aging in senior pets (Penaliggon, 1991; Kapl and Rudolphi, 1998). The efficacy of nicergoline has been demonstrated in at least one clinical trial (Penaliggon, 1991). It was recently determined that senior dogs display a greater sensitivity to the memory impairment effects of scopolamine (an anticholinergic drug) than younger dogs and show a positive response to experimental cholinomimetics (Araujo et al, 2005a). A major focus of drug therapy for Alzheimer's disease in people is to enhance cholinergic transmission. Therefore, drugs that act to augment cholinergic transmission might have application for clinical use in dogs with cognitive decline; however, no available drugs have been sufficiently investigated (Araujo et al, 2005a). This may, however, explain why some of the natural supplements (e.g., those containing phosphatidylserine) are effective by enhancing cholinergic transmission or helping protect cholinergic neurons (Vannucchi et al, 1990; Gelbann and Mullet, 1992).

In addition to preventive therapy, it may be necessary to consider medications to treat specific signs such as anxiety, restlessness, night waking and agitation. Selection of the appropriate medication should consider the pet's health and any concurrent medications. In general, anxiolytics that are less likely to cause hepatic complications (e.g., clonazepam, oxazepam, lorazepam or buspirone), natural products such as DAP, and antidepressants that have little or no anticholinergic effects, such as fluoxetine might be the most appropriate options.

REASSESSMENT

Improvements in abnormal behavior associated with brain aging may be noted within six to 12 weeks after making a dietary change. If improvements are not noted with 12 weeks, then it is unlikely that nutritional management alone will result in significant improvement. Therapy with supplements and drugs appears to be safe to use in conjunction with nutritional management. Reassessment of behavioral changes can also occur during routine health maintenance protocols established for mature or geriatric pets in each hospital.

As mentioned above, in 2005, the American Animal Hospital Association senior care task force published guidelines that recommended yearly wellness screening for healthy mid-

dle-aged pets and twice yearly screening for senior pets (i.e., last 25% of predicted lifespan). At each visit, the pet should receive a physical examination and laboratory tests and the owner should be extensively questioned about changes in behavior and health (Epstein et al, 2005). However, patients with health problems and those receiving drugs or medications may need to be assessed more frequently or have more extensive testing (e.g., blood pressure measurement, radiographs). For example, semiannual visits may be adequate for dogs with CDS; however, if signs worsen or new signs arise, the owners should schedule a more immediate reassessment to ensure that new diseases are not emerging and to assess whether additional therapeutics might be needed. When drugs are dispensed, followup visits should be scheduled based on the specific drug and disease. For example, dogs receiving selegiline should be reassessed after the first month, whereas dogs receiving most nonsteroidal antiinflammatory drugs should be reassessed within a few weeks to establish therapeutic effect and reassess liver enzyme activity.

ENDNOTES

a. Prescription Diet b/d Canine. Hill's Pet Nutrition Inc., Topeka, KS, USA.
b. Senilife. Innovet Italia S.r.l., Milano, Italy.
c. Novofit Product Profile. Virbac Corporation, Fort Worth, TX, USA.
d. Anipyrl. Pfizer Animal Health, Exton, PA, USA.

REFERENCES

The references for **Chapter 35** can be found at www.markmorris.org.

CASE 35-1

Behavioral Changes in an Older Beagle

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Patient Assessment

A 13-year-old intact female beagle was admitted for routine health maintenance procedures. The owners reported no obvious health problems with the dog other than halitosis and masses under the skin of the ventral abdomen. As part of the geriatric health maintenance program administered at this hospital, the owners were asked to complete a behavioral questionnaire and checklist (**Table 35-1**). On this questionnaire, the owners noted that the dog had shown decreased greeting behavior when they returned home, had less interest in being petted by the owners or their children, paced aimlessly in the fenced backyard at times, often refused to play with the younger dog at home and occasionally woke up at night and paced in their bedroom. The owners attributed these changes to aging and did not consider them major problems.

Physical examination revealed a geriatric dog with a body weight of 12.0 kg and an ideal body condition score of 3 on a 5-point scale. Abnormalities include moderate periodontal disease with extensive bilateral calculus formation on the premolars and molars and reddening and mild swelling of the gingival margins, a small, soft 2 x 2 cm subcutaneous mass at the left sternal border and a small, firm mammary tumor in the third right gland.

Routine preventive health testing included a complete blood count, serum biochemistry profile, heartworm check, urinalysis, fecal examination and fine-needle aspiration of the two masses for cytologic evaluation. Results of blood work, parasite exams and urinalysis were normal. Fine-needle aspiration cytology was consistent with a lipoma and benign mixed mammary tumor.

Assess the Food and Feeding Method

The dog was fed a combination of dry and moist commercial grocery brand dog foods supplemented with occasional table scraps.

Questions

1. What are potential causes and ways to evaluate the behavioral problems noted in this dog?
2. Outline a comprehensive medical and nutritional management plan for this patient.

Answers

1. Aged dogs are susceptible to a number of neurologic disorders with a wide variety of clinical presentations. Behavioral changes, alterations in mental status, seizures, loss of vision or hearing, pain, tremors, stiffness, weakness, gait abnormalities and motor dysfunction are associated with a variety of neurologic diseases. A screening neurologic examination that evaluates mental status, cranial nerve function and gait often can detect neurologic deficits. When deficits are present, a complete neurologic examination

is indicated to further characterize the abnormalities and localize the lesion.

Older dogs are also at risk for developing a variety of age-related behavioral disorders. Aged dogs exhibit deficits in learning and memory similar to those in people, and the underlying mechanisms that produce the cognitive deficits may affect behavior. Common behavioral problems in older dogs include decrements of attention and activity, inability to navigate stairs, wandering and disorientation and disturbances of the sleep-wake cycle. Older dogs lose housetraining habits and are less interactive with people, toys and other animals. Some dogs also exhibit decreased exploratory behavior. This spectrum of behavioral problems parallels many changes that occur in human dementia.

Many owners of older dogs are aware of behavioral changes but do not report them to veterinarians because they think it is part of the normal aging process. This emphasizes the importance of using behavioral or cognitive dysfunction checklists routinely as part of the screening process during geriatric health exams. In this case, the dog's owners noted mild behavioral alterations that should be discussed further.

2. As noted earlier, a neurologic examination should be performed to rule out significant neurologic disease. Normal results of routine blood, urine and fecal tests make serious underlying metabolic disorders unlikely at this time. Dental prophylaxis and excision of the masses can be accomplished during one anesthetic event. Medical and/or nutritional management can be used if brain aging and cognitive dysfunction are considered likely causes of the behavioral changes. Medical treatment includes use of drugs such as selegiline hydrochloride (Anipryl[a]) to alter brain neuropeptide levels.

   Nutritional strategies are based on studies showing that oxidative damage to the canine brain increases with age and precedes morphologic brain changes associated with cognitive dysfunction and age-associated behavioral changes. Brain tissue is especially vulnerable to free radical damage because of its high metabolic activity, high fat content, naturally low levels of protective antioxidants and limited regenerative capabilities. Foods rich in antioxidants such as vitamin E, vitamin C, and flavonoids and carotenoids from fruits and vegetables, and rich in mitochondrial cofactors such as L-carnitine and α-lipoic acid will decrease signs of brain aging, improve cognitive ability and provide noticeable change in behaviors. Laboratory studies have shown that foods rich in antioxidants and mitochondrial cofactors improve learning in older dogs with cognitive dysfunction. In clinical studies, dogs with aged-related behavioral changes consuming an enriched food showed improvements in disorientation, family and animal recognition and interaction, sleep patterns, housetraining and activity level.

Epilogue

A neurologic examination was normal and the dog was hospitalized for a dental prophylaxis and tumor excision. The patient recovered uneventfully from these procedures and was discharged with Prescription Diet b/d Canine.[b] The dog's owners were instructed to feed the food enriched with antioxidants and mitochondrial cofactors for at least three months and then return for further evaluation. They were also instructed on how to brush the dog's teeth and appropriate oral care products were dispensed for home use. Phone calls to the owners over the next couple of months confirmed that they were brushing the dog's teeth, feeding the enriched food exclusively and that some behaviors were improving. At the three-month recheck examination, the patient's owners reported that the dog was wagging its tail for the first time in many years, was interacting with family members and the other dog more often and sleeping through the night without waking or pacing excessively.

Acknowledgement

Thanks to Joe Hosey of Topeka, KS, for providing case information.

Endnotes

a. Pfizer Animal Health, Exton, PA, USA.
b. Hill's Pet Nutrition Inc., Topeka, KS, USA.

CASE 35-2

Extending the Length and Quality of Life of an Aging Female Bichon Frise

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Patient Assessment

A 15.5-year-old, spayed female Bichon Frise was presented for euthanasia due to its age, multiple behavioral signs, its owner's age, financial considerations and household factors, which included the inability of a single elderly women in a small detached home to live with the dog's poor health and behavior. Previously, the dog received regular, quality care throughout its life.

At age 10, the dog developed calcium oxalate uroliths, which were removed surgically. Following surgery the dog was fed Prescription Diet u/d Canine[a] as an aid in preventing recurrence of uroliths. At age 12, the dog required surgery to repair a ruptured cruciate ligament. At age 14, the owner began to report a decrease in activity and responsiveness to stimuli. On examination, the dog had moderately decreased vision and some arthritis in the leg that had been surgically repaired. Results of all laboratory tests (complete blood count, serum biochemistry profile, urinalysis, endocrine screening) were within normal limits; no other physical abnormalities or neurologic deficits were identified. Because no other cognitive signs were evident, a nonsteroidal antiinflammatory drug (meloxicam) was prescribed for the stifle arthritis, which improved the dog's activity and mobility and the dog appeared to adapt well to its decreasing vision.

One year later, at age 15, the dog was presented because of newly emerging multiple behavioral signs. With the aid of the cognitive assessment table (**Table 35-1**), the owner reported an increase in anxiety, agitation, restless pacing, house soiling, a decreased responsiveness to stimuli and alterations in sleep with shorter, more frequent sleep periods during the daytime and waking throughout the night. All laboratory tests were within normal limits. Physical and neurologic examinations were also unremarkable except for the previously diagnosed vision loss and stifle arthritis. A neurologic referral and magnetic resonance imaging were declined; however, the owner consented to a selegiline[b] trial. Over the next two months, the owner noticed an increase in the pacing and house soiling, a further decrease in awareness, decreased responsiveness to the owner, a decline in hearing, a decreased tolerance to being left alone and a loss of learned commands. The dog also developed signs of colitis and intermittent vomiting. The owner discontinued the selegiline, which did not appear effective at controlling any of the behavioral signs, and then discontinued the meloxicam. Although the vomiting resolved, the colitis persisted.

Assess the Food and Feeding Method

The dog was fed one-half cup and one-half can of Prescription Diet u/d Canine daily.

Question

At this point, considering the uroliths were no longer a priority, could a trial of Prescription Diet b/d Canine[a] ameliorate some of this patient's behavioral problems before any final decisions were made regarding euthanasia?

Answer

A urinalysis and a fecal examination (to rule out parasites) were the only tests approved by the owner; results were within normal limits. The dog began to show some improvement within the first week of changing to Prescription Diet b/d Canine. At the end of two months, the owner reported that the dog was more aware, active and interactive with its owner and that wandering had decreased. The dog slept through most nights and was able to be retrained to paper to eliminate the house soiling. The owner also reported that the dog was barking at squirrels and other stimuli that passed the property, which it had ignored for more than two years. Therefore, an improved awareness and responsiveness to stimuli seemed to be emerging despite the apparent decline in vision and hearing. The owner also commented that the dog's stools were regular; however, the dog was experiencing increasing hind-leg discomfort as mobility increased. A glucosamine hydrochloride/chondroitin sulfate combination (Cosequin[c]) was dispensed because the owner was unwilling to try other pharmaceutical options.

Epilogue

The dog was maintained on Prescription Diet b/d Canine and Cosequin for almost a year before problems again began to emerge. At approximately 16.5 years of age, the dog was presented for evaluation of hematuria, decreased activity and further deterioration of vision and hearing. The owner reported that the dog was again more anxious, pacing when awake, seeking out the owner more, increasingly disoriented and sleeping much more. House soiling and waking at night had not recurred. The hematuria was caused by bacterial cystitis (with no evidence of calculus recurrence), and the arthritis and sensory decline were likely responsible for some of the decrease in activity levels. Euthanasia was discussed; however, the owner consented to concurrent trials with antibiotics and

Senilife.[d]

After one month, the owner reported that the dog was far less confused. It had been going to the opposite side of exit doors but was now entering and exiting properly. It was also more active and alert, sleeping less during the day, less dependent on the owner and appeared to be more aware of visual stimuli and odors. The dog maintained this improvement for several months but was euthanized at the age of 17, primarily due to extensive loss of vision and hearing, hind-leg weakness, inability to interact with its owner and find its paper for elimination.

In this case, the ongoing assessments (i.e., the cognitive assessment table [**Table 35-1**]), and interaction between the dog's owner and the veterinarian allowed for therapeutic adjustments. It might have been justified to intervene with a food such as Prescription Diet b/d Canine at an earlier age; however, preventing recurrence of uroliths had initially been a greater priority. When multiple problems exist, dietary decisions must be made according to the condition with the highest priority. Therefore, in this case, the patient was maintained on Prescription Diet u/d Canine and a drug approach (selegiline) was used for the behavioral problems. When selegiline was ineffective and the cognitive signs advanced, changing to Prescription Diet b/d Canine became the higher priority. Additionally, the pharmaceutical regimen may have contributed to the increase in wandering and gastrointestinal side effects. Selegiline is metabolized to amphetamine, which is expected to increase activity, and meloxicam is known to aggravate gastrointestinal problems. Additionally, some nonsteroidal antiinflammatory drugs may increase brain deposition of beta-amyloid. In addition, S-adenosyl-methionine may be useful to treat cognitive dysfunction in elderly pets.[e] It is also interesting to note that this was the first case in which the veterinarian saw improvement in cognitive signs with Prescription Diet b/d Canine but not selegiline.

By regularly and immediately attending to emerging health problems, monitoring each new therapeutic agent for effects and side effects and changing or adding new therapeutic options, the owner and veterinarian helped to maintain the patient's longevity and quality of life for almost seven years from the first onset of clinical problems.

Endnotes

a. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Pfizer Animal Health, Exton, PA, USA.
c. Nutramax Laboratories, Inc., Edgewood, MD, USA.
d. Innovet Italia S.r.l., Milano, Italy.
e. Novofit Product Profile. Virbac Corporation, Fort Worth, TX, USA.