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INTRODUCTION TO PURINA™ SYMPOSIUM 2018

Purina has always been a strong supporter of veterinary education, and we are very proud to have organized the Purina Symposium "From learning impairment to epilepsy. What behaviourists and neurologists can learn from each other." to contribute to the dissemination of knowledge and allow for network building in the veterinary community.

Cognitive health is an important area of research for Purina, as it has a great impact on the lives of both pets and their owners. For this reason, this Purina Symposium aims to provide a holistic approach to the management of disorders that affect cognitive health, by bringing together experts in the fields of animal behavior and neurology. We believe the different points of view from these leading scientists will allow us to see a bigger picture and help us gain insight into the management of related disorders such as CDS (cognitive disorder syndrome). Research and development in this area is key to provide our pets with a better quality of life.

Purina has undertaken extensive studies on how to improve cognitive function with nutrition, formulating special diets for ageing animals. Together with the proper diagnosis, environmental enrichment and pharmacological management, we can help our ageing pets lead a happier life.

Rosa Carbonell
Head of the Veterinary Channel

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COMPLEX SIMPLICITY
HOW TO BETTER MANAGE EPILEPSY AND ITS COMORBIDITIES

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Holger is currently the Head of Department of the Clinical Science and Services at the Royal Veterinary College, Professor of Veterinary Neurology and Neurosurgery and the Past-President of the European College of Veterinary Neurology. He graduated from the Veterinary School of Hanover in 2001, where he also did his PhD in Neuropharmacology studying basic mechanisms of drug-resistant epilepsy. He then completed his specialist clinical education doing an internship and a residency in Neurology and Neurosurgery at the RVC. Holger is internationally known for his work in the field of Chiari-like malformation/syringomyelia and epilepsy. Holger has been chairing the International Veterinary Epilepsy Task Force, which published recently seven consensus statements for canine and feline epilepsy and was a co-chair of the recent published ACVIM consensus statement about medical treatment of epilepsy. He has been a recipient of several Jim Bee educator excellent in teaching awards, the prestigious Bourgelat Award from BSAVA and the International Canine Health Award from the Kennel Club. He has published multiple books and book chapters, more than 180 articles, more than 120 conference abstracts, and is a frequent flyer on the international conference circuit.

When neurologists and first opinion practitioners think epilepsy, they think seizures and how to best control them. Epilepsy is, however, far more than a simple seizure disorder being managed with antiepileptic drugs (AEDs). Epilepsy is a brain disease[1] with seizures being the salient clinical sign of the disease process. Epilepsy and its drug management has been associated with comorbidities such as cognitive dysfunction and behavioural changes[2-4]. The prevalence of psychiatric disorders is increased in people with epilepsy. It is higher than in either the general background population or patients with other chronic medical disorders[5-7]. Depression and anxiety disorders, followed by psychoses and attention-deficit disorders are the most frequently reported psychiatric disorders[6,8-11]. A bidirectional relationship between psychiatric disorders, such as depression and epilepsy has been suggested, with potentially mutual operant pathophysiological mechanisms[12]. This observation is supported by patients with epilepsy being at greater risk of developing depression, but patients with depression also being at higher risk of developing epilepsy[13,14].

Behavioural comorbidities of epilepsy should be taken seriously due to their potential to decrease quality of life (QoL). In a study of health related QoL (HRQoL) in people with epilepsy, inter-ictal anxiety and depression were found to have adverse effects on HRQoL, with their effects greater than those of seizure frequency, severity and chronicity[15]. To date, few studies have considered the possibility of psychiatric co-morbidities in dogs with idiopathic epilepsy (IE). The first study of this topic was carried out by our research group, where it was found that at least one behaviour had changed since the onset of IE in 71% of all dogs studied[16]. Drug-resistant dogs were found to have a greater amount of unfavourable behavioural changes than drug responders in the same study[16], a finding also seen in rodent models of epilepsy, where drug-resistant rats had greater behaviour changes[17]. The main behaviour change reported in dogs with IE is anxiety[16,18], but also, attention deficit hyperactivity disorder has been recognised[19,20]. As such, epilepsy management should in the future not only focus on reducing seizures, but also, consider reducing the effects of potential behavioural comorbidities[21].

As such, epilepsy management should in the future not only focus on reducing seizures, but also consider on reducing the effects of potential behavioural comorbidities[21].

In human medicine, certain AEDs have been suggested to cause anxiogenic and anxiolytic effects in some patients[21]. Most epilepsy trials have focused on controlling seizures rather than monitoring behaviour comorbidities. Studies are often small scale with high variability in methodology conflicting in their results. Veterinary medicine appears to be not much better in studies reporting, the anxiogenic or anxiolytic effect of AEDs in dogs, and is and is therefore challenging to reach conclusions. A recent systematic review and meta-analysis of AED's tolerability and safety found that 10% of dogs treated with primidone had anxiety reported as an adverse effect, but there

were no reports of increased anxiety in dogs receiving phenobarbital, potassium bromide, levetiracetam, zonisamide or felbamate[22]. The more commonly drugs used phenobarbital and potassium bromide have come out of favour in human medicine due to their behavioural side-effects[21]. Some of the most promising anxiolytic AEDs used in human medicine are gabapentin/pregabalin[21], but these drugs have limited evidence in regards of seizure suppressing activity in dogs with IE[23] and have not been used first-line.

The new AED imetopoin, which is licensed solely for dogs with IE, showed promising anti-seizure and anti-anxiety effects in rodent models[24] and in a seizure Beagle model[25]. Charalambous and colleagues[22] systematic review found that in one of ten studies where imepitoin was used reported reversible and dose-dependent anxiety. In a questionnaire based study of our group no anxiogenic or anxioloytic effects of imepitoin was reported in dogs treated for IE[26]. On the other hand in "non-epileptic" patient imepitoin was used successfully in the management of sound related fears[27].

As aforementioned, drug-resistant dogs with IE have more behavioural comorbidities[16]. Drug-resistant patients usually receive multiple AEDs in combination. Not all but some studies in people have identified polypharmacy as a significant risk factor for increased anxiety in children and adolescent patients[21]. However, there is also a bit of a chicken and egg situation to be considered here. Whilst some studies support that polypharmacy increases the likelihood for anxiety disorders, one must also consider that the pathophysiological basis of why a patient is or becomes drug-resistant could be the basis for the anxiety disorder as well[28].

In 2011, the International League Against Epilepsy (ILAE) established for people with epilepsy consensus statements to provide clear guidelines on the management of neuropsychiatric comorbidities[29]. The ILAE recommendation is to use selective serotonin reuptake inhibitors (SSRIs) as first-line drugs for the management of anxiety in people with epilepsy. SSRIs appear to have good tolerability and most importantly, lack an effect on seizure threshold. Serotonin and norepinephrine reuptake inhibitors, benzodiazepines, azapirones, antihistamines and pregabalin have also been described as safe for the management in people with anxiety disorder comorbid with epilepsy (ADCE)[30].

The most 'famous' SSRI is fluoxetine for which there is only anecdotal evidence in veterinary epilepsy patients with ADCE. Fluoxetine and fluvoxamine both can potentially influence the pharmacokinetic properties of certain AEDs such as phenobarbital through inhibiting cytochrome enzyme activity in the liver. If they are used it is recommended to monitor the AEDs' serum levels more closely. Sertraline has been suggested as a safer substitute, which has been described for the usage of dogs with anxiety[21]. SSRIs will take more than a month to show and effect for ADCE. In some reports it has been shown that successful management of ADCE can also improve seizure control. Tricyclic antidepressant and monoamine oxidase inhibitor should be seen as second choice due to either the potential negative effect on the seizure threshold and stimulating behavioural effect respectively[21].

An interesting alternative to medication is the use of diet to modify behaviour. A significant reduction in chasing behaviour (a potential indicator of canine ADHD-like behaviour) was documented with a medium-chain fatty acid enriched diet[31]. Furthermore, a reduction in stranger-directed fear was noted in the same trial, which may indicate anxiolytic properties of the MCT.

Ketogenic diets (KDs) have shown their efficiency in reducing seizure frequency in people with epilepsy and animal models of epilepsy. Ketone bodies (acetone, acetoacetate, and ß-hydroxybutyrate) can support 60% of the brain's energy requirements and have been shown to be increased in the brain of patients consuming a KD[32]. Changing brain metabolism has been one explanation why KDs can improve seizure control. The original ketogenic diet, characterized by its high fat and low carbohydrate content, has been used for many years successfully in children with drug-resistant epilepsy, even allowing reduction or cessation of AED in some patients[33,34]. The diet is also efficacious in adult patients but compliance to the traditional KD is poor due to the high fat and low carbohydrate content of the diet. The original human KD can induce ketosis in people, but not as easily in dogs[35]. Its effect in dogs were therefore questionable. A traditional high fat low carbohydrate/protein KD failed to improve seizure control in dogs[36]. A more promising KD is based on medium chain triglycerides (MCT) which improved seizure control in the majority of cases[37]. MCTs have a high ketogenic yield which can improve brain metabolism. Furthermore, valproic acid, an AED, is an MCT and it is thought that its metabolites and other MCTs might have a similar antiepileptic effect. There is also now robust evidence that the MCT decanoic acid (capric acid; C10) has anti-seizure effects, with a recent ground-breaking study revealing its mechanism of action. Decanoic acid was found to be a non-competitive AMPA receptor antagonist at therapeutically relevant concentrations, in a voltage- and subunit-dependent manner, that results in direct inhibition of excitatory neurotransmission, and thus has an anticonvulsant effect[38]. This is especially interesting, as most AEDs used in veterinary medicine work on increasing the function of the inhibitory brain pathways, which can also explain the side effects frequently seen such as sedation and ataxia[39,40]. Decanoic acid has been shown to readily pass the blood brain barrier with 60-80% of its serum concentration arriving in the brain[41]. Interestingly, in experimental seizure models in which the direct seizure reducing effect of decanoic acid has been shown to be effective, high concentration of acetone or beta-hydroxybutyrate has no effect[38]. This could suggest that the effect on the AMPA receptor is the main mechanism of action for an MCT diet. Another interesting potential mechanism could be explained by decanoic acid regulating mitochondrial proliferation[42] and therefore protecting against mitochondrial dysfunction, which can

Interestingly, in experimental seizure models in which the direct seizure reducing effect of decanoic acid has been shown to be effective, high concentration of acetone or beta-hydroxybutyrate have no effect[38].

be seen with intensive seizure activity. The effect on improved mitochondrial function could also be recently shown by a study in our lab highlighting de-novo fatty acid generation of C17, potentially being responsible for some anti-seizure effects[43].

An MCT enriched diet was tested in a 6-month prospective, randomized, double-blinded, placebo controlled crossover dietary trial in chronically antiepileptic drug treated dogs with IE[37]. The dogs were randomised to either start on the MCT or placebo diet and were switched over to the other diet after a 3-months period respectively. Seizure frequency, severity, physical and neurological examination findings, drug serum concentrations and clinical pathology data were recorded and analysed for all dogs with IE completing the study. The overall seizure frequency was significantly reduced by 13% on the MCT diet in comparison to placebo diet; 71% of dogs showed a reduction in seizure frequency, 48% of dogs showed a 50% or greater reduction in seizure frequency and 14% of dogs achieved cessation of seizures. As many dogs experienced cluster seizures, the number of seizure days was also assessed which also significantly decreased on MCT diet. The MCT diet resulted in significant elevation of blood beta-hydroxybutyrate concentrations in comparison to the placebo diet, but no significant differences were found for AEDs serum concentrations, visual analogue scores for sedation, ataxia, QoL, weight and most laboratory values (there was only a mild decrease in creatinine and mean cell Hb concentration on MCT diet).

On a dietary trial with an MCT rich diet, 71% of dogs showed a reduction in seizure frequency, 48% of dogs showed a 50% or greater reduction in seizure frequency and 14% of dogs achieved cessation of seizures.

In addition to the demonstrated benefits of MCTs on seizure frequency, there are potentially beneficial effects on the behavioural comorbidities seen in canine epilepsy. A pilot study in children with autism showed an improvement in some of the social interaction, behavioural, and cognitive insufficiencies seen in these patients[44]. In dogs, diets have been reported to modify certain types of behaviours[45], for example certain types of aggression can improve on a low protein diet[46,47]. Interestingly, a similar MCT diet as used in the aforementioned epilepsy trial in dogs[37] has previously been shown to support cognitive health of ageing dogs[48]. The authors hypothesized that the improvement in cognitive function can be explained by the diet providing the aged brain with a more effective energy source[48].

Interestingly, cognitive impairment and cognitive health might also need to be more considered when managing epilepsy patients. Emerging research has highlighted signs of cognitive impairment in dogs with epilepsy such as reduced trainability[49], increased signs usually associated with canine dementia[4] and deficits in spatial memory[3]. Dogs with epilepsy were found to be less trainable than control dogs[49]. Dogs with epilepsy found it harder to obey a sit or stay command, were slower to learn new

tricks, were more easily distracted by interesting sights, sounds or smells, and were less likely to listen to their owner or pay attention to them. Within the group of dogs with epilepsy, AEDs were found to worsen behaviour, particularly the medications potassium bromide and zonisamide, along with the use of multiple drugs simultaneously. In the second study, dogs with epilepsy were found to show more signs of cognitive dysfunction ('canine dementia') than control dogs[4]. Dogs with epilepsy more commonly failed to recognise familiar people, had difficulty finding food dropped on the floor, and paced or wandered without direction or purpose. These signs were seen in young epileptic dogs under 4 years of age, and are thus unlikely to represent classic canine dementia seen in geriatric patients, usually seen in dogs older than 8 years of age. Within the group of dogs with epilepsy, those with a history of cluster seizures or a high seizure frequency were most likely to show these signs, which may reflect progressive brain damage from recurrent seizures. In the most recent study[3], using a task developed to practically measure signs of cognitive dysfunction in a clinical setting, dogs with epilepsy were found to show reduced performance in a spatial memory task than matched controls. While most control dogs were able to immediately find a food reward in a room after a short period of 'forgetting time', dogs with epilepsy spent longer searching for the reward.

IN CONCLUSION, epilepsy is far more complex brain disease than formerly thought. As research emerges about its comorbidities our management considerations have to improve. At the end it is all about improving QoL of the patient and the owner, which can be achieved with a more holistic approach considering all factors involved.

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JUST OLD DOG ECCENTRICITY OR AN IMPRISONED BRAIN: CANINE COGNITIVE DYSFUNCTION WRAPPED UP

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Mette Berendt graduated and received her PhD (in 1998) from the Royal Veterinary and Agricultural University (now University of Copenhagen), Denmark. Hereafter she continued as an academic staff member at this institution. Currently she is Professor and Head of Section for Surgery, Neurology & Cardiology at the Department of Veterinary Clinical Sciences, University of Copenhagen. This includes running a busy Neurology Referral Service and research group at the University Companion Animal Teaching Hospital.

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INTRODUCTION

Not all dogs are successful agers. As humans, man's best friend can suffer from impaired cognition and disturbing changes of personality. Comparable to what Alzheimer's disease (AD) relatives experience, it is truly sorrowful for owners to witness their dog deteriorate. Over the last decades, it has become clear that senior dogs can suffer from Canine Cognitive Dysfunction (CCD), which in literature has also been described under names such as Cognitive dysfunction syndrome (CDS), Canine Cognitive Dysfunction Syndrome (CCDS), Canine counterpart of senile dementia of the Alzheimer's type, Canine Dementia and senility. CCD is a disease of the brain – a neurodegenerative condition that shares certain similarities with early stage human AD with respect to both the clinical manifestations and the progressive neuropathology responsible for the disease manifestations. Extracellular accumulation of the protein beta-amyloid (Aß) in the cortical neuro-parenchyma and vessel walls, cortical atrophy due to neuronal loss, dysfunction in the neurotransmitter systems, neuro-inflammatory responses, and increased oxidative damage are factors believed to contribute to the pathophysiological processes in brains of CCD sufferers.

In fact, many owners do not seek veterinary advice at all, thinking that this is just old dog eccentricity

NEUROPATHOLOGY

The neuropathology of CCD is quite comparable to that of early AD. The majority of studies concerning CCD have demonstrated a positive correlation between total Aß plaque burden and the severity of cognitive deficits. A recent study from our group did however find that both immunohistochemically and biochemically measured levels of Aß pathology in prefrontal cortex showed a consistent positive correlation to age, but not to cognitive deficit severity. An age-related maturation process of Aß deposits including large cloud-like plaques where plaques later progresses into smaller more condensed plaques, is present in both humans and dogs. It is also possible to classify Aß deposits in CCD brains into four specific maturation stages similar to the distribution seen for human diffuse Aß plaques. Furthermore, the sequence of Aß peptides in the canine species is identical to the human sequence, and a very high sequence homology between canine and human amyloid ß protein precursor (AßPP) isoforms and mechanisms of AßPP has been demonstrated. A consistent key diagnostic finding in AD brains is intracellular neurofibrillary tangles (NTFs) containing hyperphosforylated tau protein, but such pathology does not seem to exist in CCD brains. However, intraneuronal phosphorylated tau in the absence of NFT (proposed to represent an intermediate stage of pre-tangle tau pathology), has been described.

CLINICAL PROFILE OF CCD

The major hallmarks of CCD are alterations in behaviour and daily routines. Signs may initially be subtle but worsen over time as the disease progresses. An intermediate stage between normal cognitive aging and CCD, so-called mild cognitive impairment is often present, but dog owners may not seek veterinary advice until multiple signs of cognitive dysfunction are present, and it

becomes evident that the old dog suffers from behavioral dysfunction. In fact, many owners do not seek veterinary advice at all, thinking that this is just old dog eccentricity, and this is unfortunate, as dogs and owners can be helped with counseling and various supportive initiatives.

Various cognitive domains are affected with CCD. Behavioral changes have been summarized by the acronym, DISHAAL, including disorientation, altered social interactions, changes in the sleep-wake cycle, house-soiling, altered level of activity, anxiety, and impaired learning. The authors' research have shown that common clinical signs comprise aimless wandering, staring blankly into space, altered social interactions, altered sleeping patterns (sleeping at day and restless at night), increased anxiety level and decreased olfaction translating into difficulties with finding dropped food. Other authors have also described such signs. Urinating and defecating in the house may also be a troubling problem. The clinical signs associated with CCD are certainly of great concern to the owners. Despite this, owners are often very dedicated with respect to supporting and keeping their dogs. Two Danish studies have shown that dogs with CCD do not experience a shorter lifespan than dogs in general.

A 2010 study estimated the prevalence of CCD to 14.2 % in dogs more than eight years and found that only 1.9% of these dogs had a previous CCD diagnosis from a veterinarian.

PREVALENCE

The prevalence of CCD has been estimated to 14.2-22.5% in dogs older than 8 years. The risk of CCD increases with increasing age. Although not uncommon in senior dogs, CCD is however often not recognized by neither owners nor veterinarians. A 2010 study estimated the prevalence of CCD to 14.2 % in dogs more than eight years and found that only 1.9% of these dogs had a previous CCD diagnosis from a veterinarian. This highlights the need of disseminating more information about CCD to dog owners and veterinarians. The authors suggest that a few explorative questions regarding sleeping patterns, interaction patterns, possible disorientation and newly anxiety are posed to any owner of dogs older than 8 years of age coming in for vaccinations or other consults, in order to detect CCD at an early stage.

DIAGNOSIS

The diagnosis of CCD primarily rely on identifying the presence of typical CCD signs reported by the owner and the exclusion of other conditions that may provoke similar signs. Among others, intracranial space occupying lesions, inflammatory cerebral disease, hepatic and renal disease, endocrine conditions, urinary tract disease, behavioural problems, auditory and visual deficits and pain-related behaviour may display signs mimicking CCD. MRI, CT, and by indication cerebrospinal fluid examination, is desirable in order to rule out suspected structural intracranial disease.

The diagnostic work-up include a thorough history including all signs observed by the owner, information of the previous medical record, a clinical and neurological examination, a full

hematological and biochemical profile (including thyroid function tests) and urinalysis. If test results reveal any indication of the presence of systemic or intracranial disease (other than CCD), such alternative diagnosis should promptly be pursued.

At present, grading of cognitive functioning in the individual dog is approached with observational owner-based questionnaires targeting specific behavioural alterations related to CCD. Based upon a final score, the dog is classified as being either normal, having mild cognitive impairment, or as suffering from cognitive impairment compatible with CCD. A number of diagnostic CCD questionnaires are published and available. In Copenhagen, we use more than one CCD questionnaires simultaneously in order to secure the diagnostic accuracy. We also repeat questionnaires every 3-6 months in order to monitor disease progression.

TREATMENT

There is no particular treatment or cure for CCD. The patients can however be supported by a number of initiatives such as environmental enrichment, dietary adjustments, nutritional supplements and medications addressing brain function and anxiety. Details of treatment is not described in the present abstract, as other lecturers of today's Symposium will cover this subject.

PROGNOSIS

Being a progressive condition, CCD signs will worsen and multiply over time. The severity of signs experienced by the individual dog will guide the clinician and the owner to determine when quality of life (QOL) has reached a level where euthanasia could be the most ethical, and maybe even the most caring choice. Being senior dogs, other concurrent age-related diseases may influence the decision of euthanasia. From the owners' perspective, signs such as mild disorientation and impaired learning and memory may be more easily tolerated, whereas pronounced anxiety, house-soiling and sleep-wake cycle disturbances may be very troublesome for both the owner and the dog.

For any owner, deciding to say goodbye to an old dog friend will always be traumatic, and therefore it is not fair to leave it to the owner alone to evaluate QOL. The clinician holds a very important responsibility as the professional advocate for the wellbeing of the patient. This is also, why all dogs with a diagnosis of CCD should come in for regular visits where signs of disease progression and QOL are monitored and continuously discussed with the owner.

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THE BEHAVIOURIST PERSPECTIVE AND WHAT'S THE EVIDENCE OF HOW TO IMPROVE CLINICAL SIGNS?

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INTRODUCTION AND OBJECTIVES

With increasing age, some dogs develop a neurogenerative disease that is commonly referred to as canine cognitive dysfunction syndrome (CDS). CDS has a significant effect on the welfare of affected animals, as well as on the quality of the human-animal bond. The acronym DISHAA is commonly used to refer to the main behavioural changes associated with CDS: disorientation, altered interactions with people or other animals, sleep-wake cycle alterations, learning and memory deficits (which may cause house soiling problems), changes in activity level, and increased anxiety. The characteristics of each of these behavioural changes may vary between individual dogs. For example, some dogs with CDS may show reduced activity, whereas others may walk aimlessly or show repetitive behaviours. As for learning and memory deficits, some dogs may show house soling, whereas other may fail to learn new commands or will forget previously learned ones. Ruling out medical and behavioural conditions that can cause similar changes in behaviour is essential when performing a clinical diagnosis. Management of CDS includes changes in the environment and general husbandry of the dog as well as dietary and pharmacological intervention. Environmental enrichment is now considered to be an essential part of treatment. The objectives of this paper are to discuss (1) the animal welfare implications of CDS, (2) the main differentials in the diagnosis of CDS, (3) the fundamentals and practical aspects of environmental enrichment, and (4) the basis of pharmacological and dietary treatment strategies.

In the management of CDS, environmental enrichment is now considered to be an essential part of treatment.

CDS AND ANIMAL WELFARE

Animal welfare can be defined in different ways, but there is a growing consensus that whatever the definition, it must include three elements: the emotional state of the animal, its biological functioning and its ability to show normal patterns of behaviour. Indeed, it is now widely accepted that an animal's welfare embraces its physical and mental state, and that good animal welfare implies both fitness and a sense of well-being. Since the subjective feelings of the animal are an essential part of its welfare, a logical argument is that welfare will be reduced by negative subjective states such as pain and chronic fear, for example, and that it will be improved by positive states which may result from pleasurable behaviours such as positive social interactions and play, among others.

It is suggested that CDS may reduce animal welfare through at least four mechanisms. First, dogs with CDS are likely to engage less than healthy dogs in pleasurable behaviours which would enhance their quality of life.

Second, CDS may cause an increase in anxiety and stress, particularly when animals are exposed to novelty. It is well known that the psychological component of the aversive stimuli is the main determinant of the stress response. Therefore, the animal's appraisal of the situation is a major determinant of

its response. More precisely, animals that can control and/or predict the occurrence of an aversive event show less pronounced stress responses than counterparts which are unable to do so. This is relevant in animals with CDS, as the loss of memory caused by this condition is likely to reduce the ability to predict changes in the environment and has therefore the potential to increase stress.

Third, at least some forms of anxiety (such as separation anxiety, see below) have been shown to cause a negative cognitive bias, and anxiety-related conditions are more prevalent in dogs with CDS than in healthy dogs. The term cognitive bias refers to a change in cognitive processes due to the emotional state of the animal. Recently, cognitive bias tests (and, particularly, the so-called "judgement bias tests") have been used to assess animal welfare. The rationale of these tests is that animals in a negative emotional state will tend to judge an ambiguous stimulus as if it was negative, whereas the opposite will be true for animals which are in a positive emotional state. Current evidence based on cognitive bias studies indicates that separation anxiety is associated to a long-lasting, negative affective state which undoubtedly compromises the welfare of affected animals.

Finally, it is likely that CDS may compound other problems that are frequent in geriatric dogs, particularly painful conditions. Indeed, the emotional experience of pain is modified by several factors, including the emotional state of the animal and its ability to engage in pleasurable activities. Reduced sleep quantity or quality (which is a common feature of animals with CDS) may also increase the severity of pain.

When considering CDS as a welfare problem, two main issues arise. First, it is important to provide animals that suffer cognitive impairment with an environment that does not lead to unnecessary stress. Avoiding sudden changes in the animal's routine and allowing the animal to have control over its environment seem particularly important. Secondly, the possibility to express normal behavior patterns has positive effects on the health and welfare of animals. Implementing an environmental enrichment program tailored to the needs of geriatric dogs with some degree of cognitive impairment is one of the main strategies to achieve both objectives (see section on environmental enrichment below).

DIFFERENTIAL DIAGNOSIS

As mentioned previously, behavioural changes caused by CDS have been grouped into the following categories: disorientation; changes in activity, sleep and social interactions; learning and memory deficits, and anxiety-related behaviours. As all these changes can be caused by other conditions, both medical and behavioural, a detailed protocol aimed at ruling out alternative explanations must be followed before a diagnosis of CDS is reached. For example, animals that have impaired senses, physical debilitation, or painful conditions may become more aggressive. Particular attention should be given to osteoarthritis, which is highly prevalent in senior dogs and one of the main medical causes of aggressive behaviour. Other diseases that should be considered as differential diagnoses

include renal and hepatic diseases, diabetes insipidus, Cushing's syndrome, diabetes mellitus, pancreatitis, cardiovascular and respiratory disease, and urinary incontinence.

Behavioural changes in geriatric dogs may also be caused by non-medical conditions. For example, aging may lead to changes in the hierarchical relationship between dogs living in the same household and this in turn may cause aggression. The importance of hierarchy as un underlying mechanisms of dog social behaviour has been revisited by behaviourists over the last few year and is now widely accepted that it does not play as important a role as it used to be thought in the past, particularly in the context of dog-owner relationships. At least in some circumstances, however, dogs may establish a hierarchical relationship with other dogs. Aging and, in general, debilitating conditions, may upset this hierarchical relationship and alter social interactions between dogs living in the same household.

More recently, some authors have suggested that separation anxiety results from inappropriate attachment rather than from hyperattachment.

Some dogs with CDS may show repetitive behaviours such as licking, scratching of "fly snapping". These behaviours may have medical causes and a thorough medical check-up including a neurological exam is therefore warranted. Also, anxiety is known to contribute to the development of repetitive behaviours. Owners may reinforce such behaviours if they give attention to the dog only when it is performing them.

Separation anxiety deserves a special consideration as it is a very common behavioural problem in dogs and CDS may cause an increase in its prevalence. Dogs with this disorder show signs of anxiety during the owner's absence or, in some cases, when they do not have access to the owners even if they are in the same household. The most common signs of separation anxiety are vocalizations, destructive behaviour and inappropriate elimination, and dogs may show one or a combination of these signs. Also, dogs with separation anxiety can exhibit many other signs such as anorexia, excessive salivation or changes in the activity level. It has been suggested that separation anxiety may be under-diagnosed as some dogs with this disorder may display behavioural inhibition instead of the previously mentioned signs and this can go unnoticed by the owner.

Several factors are thought to contribute to the development of separation anxiety. The most commonly accepted explanation for separation anxiety is that it results from hyperattachment of the dog to its owner. Typically, dogs with hyperattachment follow their owners around the house and constantly look for attention. The problem with the hyperattachment hypothesis, however, is that some dogs with separation anxiety do not show hyperattachment and some hyperattached dogs do not develop separation anxiety. It has also been suggested that some cases

of separation anxiety develop from contextual fear – i.e. upon experiencing a frightening experience when being alone, dogs develop fear of being left alone. More recently, some authors have suggested that separation anxiety results from inappropriate attachment rather than from hyperattachment. In fact, there is evidence in the psychiatric literature indicating that separation anxiety in children may indeed develop from inappropriate attachment. This is more likely to happen when parents fail to provide consistent and predictable emotional safety. All these hypotheses do not need to be mutually exclusive and it is likely that separation anxiety has different causes including hyperattachment, contextual fear, inappropriate attachment or even a combination of them.

Both a thorough anamnesis and recording the behaviour of the dog when left alone will help to confirm the diagnosis of separation. A medical check-up should be performed, as some medical conditions, such as blindness, for example, could contribute to the development of separation anxiety.

ENVIRONMENTAL ENRICHMENT

Environmental enrichment can be defined as a process that aims to improve the care of animals by providing environmental stimuli necessary for their welfare. Environmental enrichment techniques for animals follow one or more of the following guiding principles: (a) increasing control or contingency between animal action and environmental reaction, (b) presenting cognitive challenges such as learning what a trainer is requesting or solving a problem, (c) meeting specific behavioral needs such as need for shelter/hiding or foraging, (d) providing an environment in which exploration is stimulated and rewarded, and (e) stimulating social interaction.

Environmental enrichment is by no means a new concept and environmental enrichment is considered an essential practice to improve the welfare of animals under human care, including companion animals. Environmental enrichment has many positive effects on animal welfare, including a reduction of time spent performing stereotypies and other "abnormal" behaviours, increased overall activity and exploratory behaviour, decreased frequency and intensity of aggressive interactions, decreased prevalence of some diseases and reduction of the chronic stress response.

There are several forms of environmental enrichment that are likely to be useful in dogs with CDS and in geriatric dogs in general. For example, providing alternative or additional sensory cues (mainly olfactory) to dogs which suffer visual or hearing deficits is highly recommended, as they may help dogs cope with their environment. Physical exercise tailored to the characteristics of each individual dog is equally advisable. One of the benefits of physical exercise is an increase in hippocampal neurogenesis. Interestingly, neuron loss in dogs with CDS seems to be caused to a large extent by reduced neurogenesis, which is highly correlated with learning and memory deficits in geriatric dogs.

Providing opportunities for social interaction is equally important as there is a great deal of evidence showing

that the welfare of social animals such as dogs improves significantly when they can engage in affiliative behaviours either with humans or with conspecifics. Affiliative behaviours increase the release of oxytocin which in turn reduces the stress response. In addition, dogs are highly motivated to engage in social interactions, particularly with humans.

DIETARY AND PHARMACOLOGICAL TREATMENT

There is ample evidence showing that dietary treatment is useful in cases of CDS. Diets tailored to the needs of senior dogs are designed with the objective of providing an alternative energy source for the brain, reducing inflammation and oxidative stress, and enhancing brain function and synaptic plasticity.

Long-term supplementation with medium-chain triglycerides (MCT) can improve cognitive function in aged dogs by providing an alternative energy source for the brain. In one study, for example, aged beagle dogs in the treatment group were given a diet supplemented with 5.5% MCT for 8 months. After an initial wash-in period, treatment and control dogs were tested on a battery of cognitive test protocols. The MCT supplemented group showed significantly better performance on most of the test protocols when compared with the control. The group differences also varied as a function of task difficulty, with the more difficult task showing greater supplementation effects than the easier tasks. As the dogs in the treatment group showed significantly elevated levels of beta hydroxybutyrate, it is suggested that MCT supplementation improves cognitive function in aged dogs by providing the brain with an alternative energy source.

MCT supplementation improves cognitive function in aged dogs by providing the brain with an alternative energy source.

Reduction of oxidative stress can be achieved by providing antioxidants and mitochondrial cofactors that may decrease the deleterious effects of free radicals. The brain is particularly susceptible to the effects of free radicals, which play an important role in aging. The high susceptibility of the brain to the deleterious effects of free radicals is a consequence of the brain's high rate of oxidative metabolism, its high content of lipids, and its limited ability for regeneration. It has been shown that antioxidants improve the performance of aged rodents and there are several studies showing that an antioxidant-enriched diet improves cognitive performance in senior dogs.

As for the pharmacological treatment, selegiline is likely to be the most commonly used drug in dogs with CDS, although nicergoline and propentofylline are other recommended options as well. Selegiline is a MAO B inhibitor that increases dopamine activity and probably other neurotransmitters as well (mainly noradrenaline). In addition, selegiline has a neuroprotective effect and increases the clearance of free radicals.

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CATS ARE NOT SMALL DOGS – FELINE COGNITIVE DYSFUNCTION SYNDROME, ITS DIAGNOSIS AND MANAGEMENT

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CDS is the medical term for age related deterioriation in brain function and has many similarities with Alzheimer's disease (AD) in people. It is estimated that more than half of cats aged 15 years and over are affected by CDS[4]. The cause of CDS[4, 5] is not known but compromised blood flow to the brain and damage resulting from free radicals are believed to play a role in damaging the brain tissue. The cat's environment has an influence on both progression of CDS and protection from CDS. For example, air pollutants may contribute to oxidative damage and hence worsening of CDS. Noisy environments can be difficult for patients with CDS to cope with and may exacerbate the condition.

The most common clinical signs are behavioural changes including:

- Altered relationships and social interactions with people and other animals in the home – this can include becoming more 'clingy', aggression and withdrawing from interactions
- Learning and memory problems such as litter tray accidents – passing urine and/or faeces outside the litter box
- Signs of confusion and disorientation – appearing to be 'lost' even when in a familiar location, staring into space, wandering aimlessly, getting 'stuck' in a corner of a room
- Altered grooming behaviour (increased/ decreased)
- Reduced activity levels – exploring less
- Anxiety and irritability – seeming restless or agitated, vocalising more (especially at night)
- Altered sleep cycles – sleeping more in the day and less at night, vocalising at night

CDS is a diagnosis of exclusion – other causes of the clinical signs need to be excluded. Differential diagnoses for the above behavioural changes would include the following with those in bold considered the most likely in an elderly cat:

- **Hyperthyroidism** – irritability, anxiety and night time vocalisation are commonly encountered in cats suffering from hyperthyroidism
- **Systemic hypertension** – 'hypertensive encephalopathy' may result in similar clinical signs to CDS
- **Loss of hearing/vision** may result in behavioural clinical signs so these should be considered
- **Chronic pain** for example associated with osteoarthritis can result in some overlapping clinical signs such as aggression/withdrawal, altered grooming, altered relationships in the home
- **Space occupying lesions** such as meningioma
- Infectious diseases associated with neurological signs such as feline infectious peritonitis (more commonly diagnosed in young than old cats), feline immunodeficiency virus infection, Toxoplasmosis and so on
- Metabolic causes of encephalopathic clinical signs including liver disease, portosystemic shunts, advanced chronic kidney disease
- Urinary tract infection – in elderly people, urinary tract infections may be associated with symptoms of confusion/ dementia, rather than classic lower urinary tract signs.

These symptoms tend to be especially severe in patients with pre-existing cognitive dysfunction.

It has been suggested that elderly cats

with urinary tract infections may also show signs of confusion/dementia as one manifestation of their illness.

Behaviour questionnaires can be helpful in identifying cats suffering from CDS[1]. A full clinical history, physical examination and minimum database are needed to exclude other causes of the cognitive dysfunction.

CDS cannot be cured and should be considered to be a progressive condition – ie it will get worse with time. Clinicians should therefore do all they can to facilitate early diagnosis of this condition with the aim of providing appropriate supportive interventions.

Environmental modification, enrichment and support should be aimed at stimulating the cat to promote and maintain brain function. Play and toys can be helpful in stimulating growth and survival of nerves. Environmental enrichment should be employed when the cat is young. Unfortunately this type of environmental enrichment can be counter productive in very badly affected cats where they cope poorly with change and find play/stimulation stressful. So if play seems stressful for the cat, it is best to not pursue. Cats in this category benefit from a calm, stable environment where all of their key resources are easy to access. For the elderly cat that may have concurrent osteoarthritis, provision should be made for key resources to be readily present in all areas of the home that the cat spends time in. Key resources include water, food, rest areas, an area where the cat can hide if desired, litter trays and opportunities for play and stimulation.

Elderly cats should have access to a litter box even if their preferred toilet area has previously been outside in the garden. Easy access to a litter box helps reduce the incidence of periuria/toileting 'accidents' in the home. Low sided boxes are often easier for them to get in and out of. The ideal litter box is 1.5 times the cat's length from nose to tail base in length and contains a 3-4 cm depth of fine, sandy clumping litter.

Supplements/strategies aimed at reducing anxiety should be employed, where appropriate. This may include environmental modification, use of synthetic feline facial pheromone preparations (Feliway®, Ceva) and valerian containing diffusers (Pet Remedy™, Animalcare) as well as nutraceutical supplements such as alpha casozepine (Zylkene®, Vetoquinol).

Diets high in antioxidants and other supportive compounds are believed to reduce oxidative brain damage and help improve cognitive function [3]

Diets high in antioxidants and other supportive compounds (eg essential fatty acids, fish oils, arginine, beta carotene, Vitamins B and E) are believed to reduce oxidative brain damage and help improve cognitive function[3]. One study showed improved cognitive function in cats receiving one such diet[3].

S-adenosylmethionine (SAMe) has been assessed in a small number of cats with CDS and found helpful in those with early changes of CDS[2].

There are no licensed medications for CDS in cats although there has been interest/anecdotal benefit reported with a number of compounds including selegeline (Selgian®, Ceva), and propentofylline (Vivitonin®, MSD).

Night time vocalisation can be very distressing for carers. Tactics to aid management of this include creating a 'bedroom' for the cat to be put into at night. When the owner goes to bed, the cat is given a tasty treat/supper and put into their bedroom as well. All resources that the cat needs are also present in this room which could be the owners kitchen/bathroom/spare bedroom. A Feliway® +/- Pet Remedy diffuser may also help provide a sense of calm and reassurance for the cat. Any vocalisation is not acknowledged or rewarded by the owner. The door to the cat's room is opened in the morning when the owner gets up. These tactics usually help to reduce night vocalisation and ensure that the owner's sleep is not disturbed. In order to be a good carer, it is vital to have appropriate rest and sleep and these tactics are not being cruel to the cat.

IN CONCLUSION, CDS is a common feline complaint but is often under-recognised and under-managed. Now that knowledge on presenting signs is available, clinicians should be in a good position to diagnose and manage affected cats. This is particularly important now that better cat care is increasing the numbers of older cats and hence increasing the number of cats with CDS in all practices.

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FROM THE LAB TO THE FIELD. INSIGHTS INTO THE INFLUENCE OF DIET ON CDS

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Dr. Landsberg has received awards for his service to the profession from the American Animal Hospital Association and from the Western Veterinary Conference.

Cognitive dysfunction syndrome (CDS) is a neurodegenerative disorder of senior dogs and cats characterized by gradual and progressive cognitive decline. Advancing brain pathology is expressed by signs related to learning, memory, perception, awareness, social interactions, sleep and activity. The diagnosis is based on clinical signs described by the acronym DISH representing Disorientation, Social Interactions, Sleep-wake cycles, and Housesoiling (and other learned behaviours)[21,25]. In addition, while activity may decline with age[1], an increase in spontaneous activity is seen with greater severity of CDS[34,38,39]. Increased anxiety and agitation are also associated with CDS ranging from 46% in dogs with CDS to 4% in unaffected dogs[11]. Therefore the acronym DISHAA also includes Anxiety and altered Activity.

In a University of California-Davis study, 28% of dogs aged 11-12 years had at least 1 category of DISH and 10% had 2 or more categories, while in dogs aged 15-16, 68% had 1 category and 36% had 2 or more.

While a decline in learning and memory may be the hallmark signs, the average pet may appear minimally challenged until the dysfunction becomes severe. In fact, while pet owners most commonly begin to report changes associated with cognitive decline beginning around 11 years or older, using laboratory based neuropsychological tests, visuospatial deficits (DNMP) have been demonstrated as early as 6 years of age[5, 36, 41]. While clinical signs of CDS tend to parallel a decline in performance in these tasks, a direct correlation has yet to be established[47].

Much of the initial research into brain aging and cognitive decline in dogs has been with laboratory housed Beagles. A program which began at University of Toronto and transitioned to CanCog Technologies has focused on establishing standardized protocols for assessing cognitive decline and the effects of therapeutic interventions. Dogs are initially trained to find a food reward in open food wells and then taught to displace a single object covering the food well to recover the food. The dogs are then presented with two distinct objects, only one of which is associated with a food reward. This task, known as object discrimination learning, provides an initial measure of dogs learning ability.

Cognitive abilities change with age in a manner that varies with subjects and task. While simple discrimination learning shows relatively little change with age, performance deteriorates when objects are more similar or involve more complex learning including size discrimination, working memory (DNMP), executive function (reversal learning) and attention[47].

CARING FOR COGNITIVE HEALTH OF SENIOR PETS

Age is the primary risk factor for CDS with prevalence and severity of signs increasing with age[21]. In a University of California-Davis study, 28% of dogs aged 11-12 years had at least 1 category of DISH and 10% had 2 or more categories, while in dogs aged 15-16, 68% had 1 category and 36% had 2 or more[25]. In a recent study, over 6 months 42% of

dogs with no impairment progressed to mild impairment and 24% with mild progressed to moderate. Over 1 year, 71% converted from none to mild and 50% from moderate to severe[21]. Diet has also been shown to be a risk factor with dogs fed a lower quality home-made or grocery store food having a 2.8X greater risk than dogs fed a quality commercial food designed for age, size or health[19].

As initial signs of cognitive decline may be subtle or mild, most cases go undiagnosed until signs become sufficiently problematic for the pet or the owner[36]. In a study of 479 dogs over the age of 8, 14.2% were diagnosed with CDS but only 1.9% had been diagnosed[36]. In addition as signs of CDS may be caused by underlying medical problems, care of senior pets should include twice yearly examinations with both health and behaviour screening questionnaires and laboratory tests both to rule out medical causes of behavioural signs as well as screen for subclinical abnormalities.

ASSESSING THERAPEUTIC EFFECTS IN THE LABORATORY AND IN THE FIELD

Oxidative stress and chronic inflammation are risk factors for accelerated brain aging and Alzheimer's disease (AD) in humans, with increasing evidence that these are also contributing factors in dogs [5, 16, 22, 31, 43, 45]. Additional risk factors might include DHA deficiency[6], high homocysteine[24], low vitamin B6, vitamin B12, and folic acid[7] and high blood pressure[10]. Strategies for management and treatment of CDS might focus on reducing oxidative stress, correcting metabolic changes associated with cognitive decline, and improving mitochondrial function and neuronal health through nutritional therapeutics that address these risk factors [14, 15]. In humans, diets containing fruits, vegetables, seeds, legumes, nuts and fish oils as in a Mediterranean diet may improve cognitive function while diets containing fruits and vegetable extracts together with antioxidants and mitochondrial cofactors (alpha-lipoic acid and l-carnitine) have been demonstrated to improve cognitive function in dogs[12, 15]. Beneficial effects are also seen with exercise. In aged dogs after both acute (24h) and chronic (14 day) treadmill exercise, cognitive performance and memory consolidation was improved[40]. However, a combination behavioural enrichment and nutrition was most effective in slowing the progression and improving the clinical signs of CDS in dogs[22]. Similarly, in older women, combining MCT and aerobic exercise was more ketogenic than exercise or MCT alone and exercise enhanced the brain metabolic rate of ketone bodies but not glucose[5, 44].

THE USE OF A BRAIN PROTECTION BLEND (BPB) IN DOGS

A blend of fish oil, arginine, B vitamins and selected antioxidants (Brain Protection Blend or BPB) has been developed to address the risk factors associated with brain aging and dementia[29, 31]. Fish oil (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) might improve cognitive function by correcting DHA deficiencies and providing anti-inflammatory benefits[6, 46]. Arginine can enhance nitric oxide synthesis, which has been linked to circulation, blood pressure control and cognition[8]. B vitamins might improve cognitive function by correcting deficiencies and minimizing the risk of high homocysteine[31, 7]. Antioxidants including vitamin E, C and selenium offer

protection against oxidative damage and inflammation-induced damage in both brain tissue and blood vessels[13].

Twenty-four Beagles (9.1-11.6 years, 12 males and 12 females) were recruited into the study. Dogs were first given a battery of cognitive tests to place dogs into two cognitively equivalent groups. Dogs were then assessed over 8 months beginning with a landmark task from 7 to 99 days (where the dog learns to locate the reward under a coaster closest to the landmark) followed by egocentric discrimination learning (where the dog learns to locate food under the objects based on which side) and reversal learning (where the sides are reversed). The dogs in the brain protection blend (BPB) group showed significantly better performance than the controls on the second component (land-1) of the landmark discrimination task (landmark 1 cm from coaster) and on reversal learning of an egocentric discrimination task. The BPB resulted in significantly increased arginine, omega three fatty acids, and alpha-tocopherol. These results are consistent with a previous study in which BPB enhanced cognitive function and improved learning and memory tasks in middle aged and senior cats[29]. Similarly, a combination of high omega-3 fatty acids and B vitamins reduced cognitive decline in human subjects with mild cognitive impairment[27].

THE USE OF MCT (MEDIUM CHAIN TRIGLYCERIDES) IN DOGS

A decline in the brain's ability to metabolise glucose is a common feature of aging in animals and may contribute to cognitive decline. In dogs, brain glucose metabolism is significantly reduced at 6 years of age compared to one year of age. This is the age at which visuospatial deficits are first demonstrated in dogs [20, 41]. Reduced brain glucose metabolism is also observed in elderly humans and in AD[48]. Providing ketones as an alternative source of brain energy, in the form of MCT might therefore counteract the effects of deficits in cerebral glucose metabolism[28, 32]. Dietary supplementation with MCT increases blood levels of the ketone body beta-hydroxybutyrate (BHB)[28,32]. MCT may also enhance cognitive function by increasing concentrations of polyunsaturated fatty acids in the brain of dogs[42].

In this trial, 24 beagles aged 7.5 to 11.6 years were placed into two cognitively equivalent groups based on a battery of baseline tests. The groups were treated for 8 months with a diet supplemented with 5.5% MCT beginning with landmark tests (days 7 to 92) for learning and visuospatial function, followed by egocentric and a variable oddity task to assess attention (in which the dog has to choose an object from 2 or more distractors). The MCT supplemented group performed significantly better on the more difficult tasks including landmark 1 and landmark 2, egocentric learning and reversal and the attention task with multiple distractors. Smaller improvements that were not significant were seen in the landmark 0, egocentric discrimination and object discrimination. Average improvements were seen within 2 weeks on acquisition of the landmark task with significant improvement after 30 days. The group with MCT supplementation had significantly elevated levels of BHB[28].

CLINICAL ASSESSMENT OF AN MCT AND BPB SUPPLEMENTED DIET.

Most recently Nestle Purina assessed the effects of a diet supplemented with MCT combined with BPB in a clinical trial in dogs presenting with signs of DISHAA. The rationale for the selection use and potential efficacy of these ingredients is discussed above. In selecting the screening questionnaire, the most recently "validated" questionnaire[21] identified 17 items corresponding to DISH for screening of cognitive impairment in dogs. In this study the authors removed categories of anxiety and activity. However, studies have documented an increase in anxiety (from 4% of senior dogs with no signs to 46% of dogs with CDS) and an increase in aimless or repetitive locomotor activity with increasing CDS. Therefore, the questionnaire for this study included these two categories, together with questions from all previously published questionnaires used in prevalence studies and therapeutic trials ensure sufficient sensitivity to identify signs of all stages of decline[11, 36, 34, 39]. Subsequently with statistical analysis we have reduced the number of questions and amended the questionnaire based on internal consistency, factor analysis, test-retest reliability and correlations between questions and categories.

The MCT supplemented group performed significantly better on the more difficult tasks including landmark 1 and landmark 2, egocentric learning and reversal and the attention task

In this double blinded randomized clinical trial, dogs were placed on either a diet supplemented with 6.5% MCT and BPB (Purina® Pro Plan® Veterinary Diets NC Neurocare™), a control diet or a diet containing 9% MCT and BPB. Of 100 dogs that were included based on initial screening questionnaires and physical examination, after laboratory screening an additional 13 dogs were excluded because of underlying medical problems including renal, hepatic, Cushings, and recurrent urinary tract infections. Therefore 87 dogs (48 males and 39 females) of 52 different breeds were enrolled, with 29 assigned to each group.

At the conclusion of the 90 day trial all 6 categories of DISHAA were significantly improved in the 6.5% MCT + BPB group (23/26 improved or did not progress) with the greatest improvement in the category of social interactions. At 30 days, 5 of the 6 categories (all but sleep) had significantly improved. By comparison, for the control group at 90 days, 4 of 6 categories significantly improved but not disorientation or social interactions. At 30 days 3 of 6 categories were improved. While improvement in the control diet group may have been a placebo effect (expectation of effect), the control diet also contained some of the BPB ingredients (other than DHA, EPA, and vitamins C and E) that were above AAFCO requirements, which may have contributed to a therapeutic benefit.

For the 9% diet there was no significant improvement in most signs. This group had a higher drop out rate and therefore a smaller sample size, likely due to poorer dietary acceptance by the dogs. While both test diets resulted in an increase in DHA and EPA the levels in the 9% diet were significantly lower indicating poorer feeding compliance[30].

The benefits of the 6.5% MCT diet combined with BPB are likely a result of the combination of ingredients acting together including the higher levels of antioxidants and B-vitamins, increased omega-3 fatty acids to correct deficiencies and decrease inflammation, an optimal level of arginine to improve circulation and cognitive function, and MCT to provide ketones as an alternative source of brain energy.

ADDITIONAL NUTRITION FOR THE AGING BRAIN

Other dietary and nutritional options that have been evaluated for improving cognitive function include: a diet supplemented with fatty acids, antioxidants (vitamins C and E, beta carotene, selenium, flavonoids, carotenoids), and dl-alpha-lipoic acid and l-carnitine (Hills® Prescription Diet® b/d® Canine) which was most effective in combination with environmental enrichment [4, 22]; a supplement combining phosphatidyserine, gingko biloba, resveratrol, vitamin E and B6 (Senilife®)[3, 26]; a combination of phosphadylserine, omega-3 fatty acids, vitamins E and C, l-carnitine, alpha-lipoic acid, coenzyme Q and selenium (Activait®)[17]; S-adenosylmethionine (SAMe, Novifit®) [2, 33] and a protein found in jellyfish that acts as a calcium buffer (Neutricks®)[23]. In another study over 3 months a diet supplemented with extract of turmeric, green tea extract, N-acetyl cysteine, alpha lipoic acid, and black pepper extract led to significantly better spatial attention in aged dog[14].

IN CONCLUSION, as demonstrated in the laboratory and in clinical cases, nutrition can aid the aging brain.

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SENIOR CANINE COGNITIVE ASSESSMENT

BEHAVIOURAL SIGNS Score as 0=none 1=mild 2=moderate 3= severe Identify signs that have arisen or progressed since 8 years of age or older	**SCORE**
DISORIENTATION	
- Gets stuck or has difficulty getting around objects - Stares blankly - at walls, floor, or into space - Does not recognize familiar people / familiar pets - Gets lost in home or yard - Less reactive to visual (sights) or auditory (sounds) stimuli	
SOCIAL INTERACTIONS	
- More irritable / fearful / aggressive with visitors, family or other animals - Decreased interest in approaching, greeting or affection / petting	
SLEEP–WAKE CYCLES	
- Pacing, restless, sleeps less, or waking at night - Vocalization at night	
HOUSESOILING, LEARNING AND MEMORY	
- Less able to learn new tasks / tricks or respond to previously learned commands - Indoor soiling of urine ___ or stool ___ / decreased signaling to go out - Difficulty getting dog's attention / increased distraction / decreased focus	
ACTIVITY	
- Decreased exploration or play with toys, family members or other pets - Increased activity including aimless wandering or pacing - Repetitive behaviors e.g. circling ___ chewing ___ licking ___ star gazing ___	
ANXIETY	
- Increased anxiety when separated from owners. - More reactive / fearful to visual (sights) or auditory (sounds) stimuli - Increased fear of places / locations (e.g. new environments / going outdoors)	

Assessment was created by Dr. Gary Landsberg, CanCog Technologies in conjunction with Deborah Keyes (statistician).